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Conservative Treatment of Fractures in General Practice! This is the full title of the *242-page Symposium* in the December (Philadelphia) Number of the *Surgical Clinics of North America* . . . a Symposium that is keyed to today's needs of both physician and surgeon . . . a Symposium that will prove to be one of the most practical and helpful additions any doctor could make to his working medical library.

This Symposium is headed by Dr. E. L. Eliason and covers such subjects as General Considerations in Fracture Treatment; Fractures and Dislocations of Shoulder Girdle and Ribs; Treatment of Fractures of Humerus; Fractures about the Elbows; Fractures of Shaft of Radius and Ulna; Fractures of Lower End of Radius; Treatment of Fractures and Dislocations of Hand and Fingers; Fractures about the Hip; Fractures of Shaft of Femur; Fractures about the Knee; Fractures of Shaft of Tibia and Fibula; Fractures about the Malleolus and Fractures of the Foot.

In addition to the Symposium four other important clinics are included, making this December Number among the very finest we have ever published.

A regular feature of the Surgical Clinics of North America is the *Cumulative Index.* And now as a *new and added feature,* the final number of each Clinic year will contain a Cumulative Index, not just for one year but for *three* years, making the Surgical Clinics of North America more valuable than ever before.

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THE UNIVERSALITY OF DIABETES

A SURVEY OF DIABETIC MORBIDITY IN ARIZONA

THE FRANK BILLINGS LECTURE

ELLIOTT P. JOSLIN, M.D.

BOSTON

WITH THE COOPERATION OF THE PHYSICIANS IN ARIZONA

I believe that the incidence of diabetes should be highest in communities in which (1) the average age is greatest, (2) women predominate, (3) obesity is most frequent, (4) the proportion of Jews is greatest, (5) medical supervision is closest and (6) deaths are most accurately reported. Therefore I am puzzled to explain why the mortality from diabetes should be nearly twice as high in the United States as in Canada, when the two countries are separated only by an arbitrary line. Why should the incidence of diabetes double in the United States in the ten years 1880 to 1890 and then take thirty years to do so again—between 1900 and 1930? Why should it double in Italy and Switzerland between 1920 and 1934? Why should the death rate from diabetes in Rhode Island in 1937 be four times that in Arizona or, to make the question more general, why should the rate for Alabama, Arizona, Arkansas and New Mexico be the lowest in the country in 1937, 10 or less per hundred thousand, and that for Rhode Island, New York, Massachusetts and Connecticut be the highest, or more than 33 per hundred thousand?

Such thoughts were coursing through my mind when I received the flattering invitation of the executive committee of the Section on Practice of Medicine of the American Medical Association to deliver the Frank Billings Lecture.

An armchair statistical study of the incidence of diabetes does not appeal to me; field work does. Already there are available two excellent examples of the latter—the survey conducted in Massachusetts under the direction of Bigelow and Lombard [1] of the state board of health in 1929-1931 and that in Washington sponsored by the National Institute of Health [2] in 1935-1936.

These surveys, however, were concerned with the frequency of diabetes in areas in which its statistical mortality was reported to be highest. This left to me the opportunity to undertake field work in areas in which the incidence of diabetic mortality was reported to be the lowest. I reasoned that only good could come from such a survey, because if the low incidence proved to be correct one could concentrate on a study of the cause for this immunity and might even encourage hereditarily predisposed diabetic patients to migrate to such a region. Contrariwise, if the survey showed that the information was ill founded, new cases of diabetes automatically would have been disclosed and brought under treatment, lives have been spared or prolonged and the diabetic army in the United States expanded. Moreover, of still greater consequence would be the outcome, if the evidence was frankly decisive and the reported low mortality completely overthrown, because it would put a question mark before every town, city, state or, indeed, country in the world which reported an extraordinarily low death rate from diabetes.

Where should such a survey be carried on? Obviously in one of those localities in which the reported mortality from the disease was the lowest, and in 1937 the four states were Alabama, Arkansas, Arizona and New Mexico. Alabama and Arkansas were at once ruled out by me because those states are too populous and they have too many doctors to make intimate contact possible. Arizona appeared preferable to New Mexico for the purpose because during the month of February it is said to be more available for investigation, and because Arizona is particularly diversified in climate, altitude and composition of its population.

Arizona having been chosen, the problem to be solved was why Arizona had a diabetic mortality of 10 per hundred thousand and Rhode Island one of 42 per hundred thousand in 1937, with three other states in the East—New York, Massachusetts and Connecticut—having diabetic mortalities more than 33 per hundred thousand. These mortalities were evidently not chance mortalities for a single year. This is shown in table 1, in which average mortalities are given for 1934 to 1938 of the states with the four highest and the four lowest rates. Here it will be seen that the higher rates range between 31 and 37 and the lower rates between 9 and 11 per hundred thousand of population, whereas the United States showed an average rate of 23.

While considering the possibility of making the survey, I sought advice and received it wholeheartedly from Dr. Herbert L. Lombard of the Massachusetts State Board of Health, who encouraged and, indeed, urged me to carry it on. I also received assistance in many ways from the Surgeon General of the Public Health Service, Dr. Thomas Parran, and from Dr. Louis I. Dublin and Mr. Herbert H. Marks of the statistical department of the Metropolitan Life Insurance Company and, finally, most valuable counsel from the editor of THE JOURNAL.

Certain contrasts between Arizona and Rhode Island first deserve mention because of their importance in explaining the wide differences in diabetic mortality. The area of Arizona is 113,810 square miles and more

Read before the Section on Practice of Medicine at the Ninety-First Annual Session of the American Medical Association, New York, June 12, 1940.

1. Bigelow, G. H., and Lombard, H. L.: Cancer and Other Chronic Diseases in Massachusetts, Boston, Houghton Mifflin Company, 1933.

2. The Magnitude of the Chronic Disease Problem in the United States, Washington, D. C., Division of Public Health Methods, National Institute of Health, U. S. Treasury Department, Public Health Service, 1938.

than 100 times that of Rhode Island, which is 1,067 square miles. In Arizona much of the land is made up of reservations for the Indians, forests, parks and mountainous regions save those penetrated by main highways, and this makes communication difficult. In 1937 the estimated population of Arizona was 409,000 and that of Rhode Island 681,000. The density of population per square mile is 3.8 in Arizona and 644 in Rhode Island. The relative number of physicians to

TABLE 1.—*States with Highest and Lowest Diabetes Mortality Rates per Hundred Thousand in 1937 and 1934-1938*

	Highest			Lowest	
	1937	1934-1938		1937	1934-1938
Rhode Island....	42.0	36.9	Alabama.....	10.6	11.0
New York.....	36.9	34.8	Arizona.....	10.0	9.8
Massachusetts...	33.7	31.5	Arkansas.....	9.2	8.5
Connecticut.....	32.5		New Mexico.....	8.1	8.6
New Hampshire..	....	32.9			

the population differs less than one might conceive, one to 772 in Arizona and one to 726 in Rhode Island, although in the urban areas in Arizona there are 27.6 physicians per 10,000 inhabitants and only 5.4 in the rural sections of the state. The population in Arizona in towns and villages less than 2,500 constitutes two thirds of the total inhabitants, but in Rhode Island a much smaller proportion. Indeed, in the latter state it is hardly fair to class the population of many of the small towns as distinctly rural. The distance across Arizona from north to south is nearly 400 miles and from east to west 340 miles, as compared with 48 and 37 miles respectively for Rhode Island.

How large a share possibilities for the medical supervision of the population count for the divergence in mortality of diabetes in the two states no one knows. Certainly it must be a factor, but in this discussion no percentage estimation of the part medical supervision plays will be adduced.

CRUDE VERSUS ADJUSTED MORTALITIES FOR AGE AND SEX

Diabetes is a disease in which the influence of the age and sex of the population is profound. These are well recognized facts. Table 2, compiled from data published by the National Health Board in its survey of 2,502,391 persons living largely in urban areas, enables one to see at a glance how misleading comparisons can be if based on crude statistical data alone. Thus only one diabetic individual can be found among 2,500 boys and girls and another among 1,700 young adults between the ages of 15 and 24 years. At these ages sex is indifferent, but above this level women predominate. At the age of 65 years one man in seventy has the disease and one woman in sixty. In Massachusetts over the age of 45 there is 1.1 female for every male. In Arizona the comparable figure is 0.73. Thus the simple adjustment by age and sex of the population in Arizona and Rhode Island resulted in the year 1937 in changing the ratio of diabetes between the two states from one to four to one to three, and, for the years 1929 to 1931 the crude ratio of one to three and five-tenths when adjusted to the census of 1930 falls to one to two. These standard compilations, therefore, made the task of explaining the difference in mortality less formidable, because with this aid half of the hurdles are passed.

CONTRIBUTORY CAUSES OF DEATH IN ARIZONA AND MASSACHUSETTS

The large number of deaths from tuberculosis in Arizona, 802 in 1939, compared with fifty-seven from diabetes furnished a chance opportunity to explain its statistically low diabetic mortality. Tuberculosis takes precedence over diabetes. If it could be demonstrated that as many patients with tuberculosis had diabetes in Arizona as in Massachusetts there would be a great accession in diabetic mortality data. In order to determine this, copies of Arizona death certificates bearing the diagnosis tuberculosis were made, and these were analyzed under the supervision of Dr. Lombard, but the results indicated only a fraction as many cases of diabetes among the tuberculous in Arizona and in fact all other groups in which diabetes occurred as a secondary cause, as in Massachusetts. For combined contributory causes the figure for Massachusetts was 11.3 per cent and for Arizona only 1.4 per cent. Such a striking difference suggests that in Arizona diabetes as a secondary cause of death frequently is omitted from the death certificate.

FIELD WORK

Statistical computations have changed the difference in ratio of diabetic mortality between Arizona and Rhode Island from one to four to one to two. To turn now to diabetic field work, the plan of campaign adopted was a direct outgrowth of a phrase, "the fecundity of the aggregation," once used and elaborated on in an informal evening discussion in his home, and later published, by Prof. Josiah Royce of Harvard.[3] By it he meant that, when people get together and discuss things, something new and better is likely to arise than any one of the individual members of the group is capable of producing alone. The question, therefore, uppermost in my mind was how I could secure this "fecundity of the aggregation" in Arizona. That was quickly solved, because first of all the Arizona Board of Health put its office, its staff, its publication and its good will at my disposal, and this action was quickly followed by that of the Arizona State Medical Society. In addition, I was given the help of the Veterans' Bureau facilities and Indian bureaus, and every particle of red tape was cut. Not only did the press of Arizona speak favorably

TABLE 2.—*Ratio of Diabetes in the Population*

Age	Males	Females
0-14.....	1:2,500	1:2,500
15-24.....	1:1,700	1:1,700
25-34.....	1:1,100	1:900
35-44.....	1:500	1:300
45-54.....	1:225	1:125
55-64.....	1:100	1:50
65 and over.....	1:70	1:45

These data, adapted from the National Health Survey, are based on 9,182 diabetic patients in a surveyed (urban) population of 2,502,391 persons.

of the study but their medical editor put in newspaper form the crude talks on diabetes which I had labored to devise and, finally, the pharmaceutic association of the state reduced the price of the solution used for the Benedict test for two months so that there would be no excuse for doctor or layman to be deprived of an examination of the urine. The Phoenix Pathological Laboratory reduced its fees for blood sugar tests to a wholesale minimum.

With all these agencies aiding and abetting the diabetic survey, I sent airmail letters to each doctor in

3. Royce, Josiah: Science **39**: 551, 1914.

the state asking him if he would report by name or initial the diabetic patients under his care, and I confess also to the effrontery of asking him to tell me whether he himself had diabetes. The airmail letters were supplemented by two trips to Arizona and a three weeks stay in the state during which I traveled from Yuma to Ganado, from Douglas to Flagstaff; in fact, I visited all communities in the state with a population of more than 3,000 save two, and many of the smaller towns.

TABLE 3.—*Arizona and Rhode Island Populations per Square Mile and Crude and Adjusted Diabetic Mortalities, 1937 and 1930-1938*

1937	Population per Square Mile	Physicians to Population	Diabetic Mortality per 100,000			
			1937		1930-1938	
			Crude	Adjusted	Crude	Adjusted
Arizona.....	3.8	1:772	10.0	13	8.8	10.1
Rhode Island....	644.0	1:726	42.0	37	28.3	22.4

The doctors I met were extraordinarily kind. Often they welcomed me at dinner or at luncheon, perhaps in a hospital where I had an excellent opportunity to meet them individually, and when I wished to travel from one locality to another they would transmit me at a speed of 75 miles an hour, more or less, thus eliminating distance and taking advantage of Providence, R. I., with its speed limit of 25 miles an hour. Besides these more formal meetings I rang doorbells like any detail man and, when an elderly doctor was doubtful about his having or not having diabetes, got his specimen then and there.

In reporting the results of the canvass for diabetes in Arizona I will begin with that of small and special groups, because each yields its lesson. These groups are of especial value for comparison with similar ones elsewhere. The first is a microcosm.

Jews.—In Arizona Jews number about 2,000 (1,755 in 1937). They constitute less than one two-hundredth of the population, but when I counted Jews among all the diabetic patients reported by the doctors of the state they numbered eighteen, or about one fortieth of the total number of diabetic patients, or proportionately four or five times as many. Thus the Jewish racial incidence in Arizona is even stronger than that in Boston, where years ago there were two and one-half diabetic Jews for one diabetic Gentile, a figure based on larger numbers and, in my opinion, nearer to the truth.[4] If the 100,000 ± Mexicans now in Arizona, representing one fourth of the total population, were replaced by Jews, who show four times the total diabetic morbidity incidence, the figure for diabetic morbidity in Arizona would just about double the incidence I got for the whole state.

I sense your criticism that the Jews, like so many others of Arizona's population, are newcomers and do not fairly represent the original population of Arizona, but to this I would answer that there is very little indigenous population in that state. At a dinner of twenty-three physicians in Tucson, when I asked how many of those present were born in the state not one hand was raised. However, I grant the validity of such objections. Indeed, the opportunity to meet them was one of the reasons which led me to select Arizona as a test state for diabetes, because it has some 40,000 to 50,000 original inhabitants, namely the Indians.

In this field work among the Indians not one particle of credit is due to me. All is due to the physicians in the Indian service, who cooperated in every way possible. I cannot say enough for that service, and I know whereof I speak, because I visited Indian hospitals in Sacaton, Ganado, Fort Lewis, San Carlos and the Indian school and Indian hospital in Phoenix. By no means did I canvass all the Indians or go to all the reservations with their varied institutions, but I can say emphatically that I had most cordial responses from the Indian Bureau in Washington, its representatives in the West and individually from all the government agencies, and what I say of the Indian service I can say also of the assistance I received from the two United States Veteran Facility hospitals in Tucson and Fort Whipple. Moreover, I should also mention the cooperation of the members of the staffs of the various hospitals in mining centers, Bisbee, Jerome and Globe, who took the pains to make it possible for me to meet and question physicians living nearby, although not on their own staffs.

The high grade of medical care afforded Indians in Arizona by the United States government is not sufficiently known, even among the physicians of Arizona. I cannot praise it too strongly not only for what it is doing now but for what I know has been arranged for it to do in the immediate future.

Indians.—From Washington I learned that two Indians yearly (actually eleven Indians for the six years 1934 to 1939) were reported to have died with diabetes. In addition, among 6,331 admissions (90 ± per cent Indians) between the years 1931 and 1936 to the Sage Memorial Hospital at Ganado,[5] a private institution on the Navajo reservation, the existence of diabetes was demonstrated in one Indian. When the final count of the cards with the names of the diabetic Indians living in Arizona was made I had seventy-one, and the statistical conscience of the statistical department of the Metropolitan Life Insurance Company, which revised my data, forced me to add two more, allocating these to Indians from the total number of cases with nationality unclassified, thus making seventy-three in all.

It is not strange that so few diabetic Indians were admitted to the Sage Memorial Hospital. Their patients are young. Among 1,429 admissions during 1939, only seventy-five were past the age of 50. The age distribution is given in table 4.

The survey certainly did not include all the Indians in the state. I should think it doubtful that it included more than two thirds as a maximum and more likely only one half. Granting, however, that there was not an Indian in the state escaping the survey, and comparing the seventy-three live diabetic Indians with the two reported dying each year with diabetes, one is driven to conclude that the duration of life of a diabetic Indian in Arizona is thirty-five years or that death certificates for Indians are faulty and fail to include the word "diabetes" where it belongs as a primary or secondary cause. Furthermore, the number of Indians with diabetes in Arizona compared with the total number of diabetic patients in the state bears essentially

TABLE 4.—*Age Distribution of Patients Admitted to Sage Memorial Hospital in 1939*

Under 5 years.....	375	20 to 35 years.....	417
5 to 12 years.....	180	35 to 50 years.....	145
12 to 14 years.....	44	50 to 65 years.....	45
14 to 20 years.....	193	Over 65 years.....	30

4. Morrison, H.: Boston M. & S. J. **175**: 54 (July 13) 1916.

5. Salsbury, C. G.: Disease Incidence Among the Navajos, Southwest. Med. **21**: 230-233 (July) 1937.

the same relative proportion, 10 per cent, as do Indians to the total population. Diabetes in Arizona is just as common among Indians as among the rest of the population.

If the survey covered only two thirds of the Indians, the number with the disease would be raised from seventy-three to 109, and the duration of diabetes in an Arizona Indian would jump to fifty-four years, which of course is absurd. A physician long associated with work among the Navajos replied to my question What percentage of Navajos in Arizona ever see or come under the influence of a doctor? "From 50 to 60 per cent," and to another question, For what percentage of deaths do you suppose there is really known an accurate cause? he answered "In our area my guess would be in about 25 per cent; in the back stretches of the reservation a much smaller percentage." Comparing these statements with the two annual deaths reported for the whole state yearly, the inference is clear that death certificates are lacking in accuracy. In fact, for the state as a whole the number of certificates filed "cause of death unknown" exceeds by several times those returned with the diagnosis of diabetes.

Doubting Thomases may say that the Indians had glycosuria but not diabetes. To this I reply that, of the first twelve blood samples sent to the Phoenix Pathological Laboratory from one of the Indian reservations because of suspected diabetes, eleven of the twelve showed hyperglycemia. Again I wish to give credit to the liberality of that laboratory in making these and many other tests for me at so minimal a sum, at what I like to call "wholesale rates." It represents another example of the "fecundity of the aggregation."

The distribution of Indians by tribes is shown in table 5 and by age in table 6. I would point out that the Navajos are nomads and the Apaches herdsmen, and the Pimas depend on agriculture and I understand harvest their crops on shares, allowing the Papagos to do most of the work.

TABLE 5.—*Diabetes Found Among Arizona Indians*

Total number of diabetic Indians found	73
Males	42
Females	29
Unspecified	2
Classification by tribes:	
Pimas	21
Apaches	12
Papagos	10
Mohaves	8
Navajos	4
Maricopas	3
Yavapai	2
Comanche	1
Laguna	1
Unspecified	11*
	73

* Two were added in allocating incomplete case reports.

TABLE 6.—*Distribution by Age and Sex of Arizona Diabetic Indians*

Ages	Males	Females
5-14	1	0
15-24	1	1
25-34	4	7
35-44	10	7
45-54	14	7
55-64	9	6
65-74	2	1
75 and over	1	0
	42	29

Two were added, allocated from incomplete cases, no sex given.

DIABETES AMONG PHYSICIANS IN ARIZONA AND RHODE ISLAND

If diabetic mortality statistics are even an approximately accurate index of the incidence of diabetes in a community, one would expect this to be reflected in the incidence of diabetes among physicians. Therefore an investigation of diabetes occurring in doctors was made in Arizona and later, to test the validity of the comparison of its low diabetic mortality of 10 per hundred thousand with that of 42 in Rhode Island, or as adjusted for the two states for age and sex, 13 and 37, a similar survey was carried out in exactly the same way and among the same number of doctors in Rhode Island. If diabetes is one fourth or one half as frequent in Arizona as in Rhode Island, the signed testimonies of the physicians in these states do not show it. The results were practically identical. In each state requests were sent to 562 doctors, and to those who did not reply to the first request a subsequent letter was forwarded. Three hundred and thirty-nine doctors reported in Arizona and of these there were eight with diabetes, or a ratio of one diabetic doctor to forty-two nondiabetic doctors. In Rhode Island the responses were somewhat more liberal. In all, 392 physicians have so far reported and eleven stated that they had diabetes, making a ratio of one to thirty-six. The average age of the doctors reporting no diabetes in Arizona was 47 years and in Rhode Island 49 years, whereas the average age of those with diabetes in Arizona was 62 and in Rhode Island 61 years. Diabetes does not spare doctors in Arizona.

TABLE 7.—*Comparison Between Diabetic Physicians in Arizona and Rhode Island*

	Arizona	Rhode Island
Total physicians	562	938
Physicians in survey	562	562
Total reporting	339	392
Diabetic	8	11
Average age	62.0 years	61.0 years
Nondiabetic	323	381
Average age	47.3 years	49.1 years
Diabetic to nondiabetic physicians	1:42	1:36

An estimate of the morbidity of diabetes among physicians in the United States can be made by a study of the deaths from the disease as reported by the American Medical Association.[6] These amounted to ninety-one for the year 1939. The total number of doctors in the country at that time was stated to be 169,682. There was, therefore, one death of a doctor with diabetes for each 1,891 physicians. If we assume that the duration of the diabetes among doctors is ten years, then the number of physicians living in the United States with diabetes would be one in 189. If we further assume a duration of twenty years, it would be reduced to one in ninety-four. Therefore, among the 562 doctors in Arizona one would expect three with diabetes on the basis that doctors lived ten years or six with diabetes if they lived twenty years. As a matter of fact, eight doctors were found in Arizona with diabetes, or one diabetic doctor for every forty-two physicians, or fully up to expectations. Of course, I am dealing with small numbers.

6. Obituaries of Physicians Published in 1939, editorial J. A. M. A. **114**: 1362 (April 6) 1939.

DIABETES AMONG CLERGYMEN IN ARIZONA

Doctors and ministers in Arizona are approximately equal in number. Curiosity led me to attempt a survey of the incidence of diabetes among the clergy. The replies were far less numerous. Thus, of 531 clergymen only eighty-eight responded, and only two of these stated that they had diabetes, a ratio of one to forty-four. However, other methods of investigation disclosed three more ministers with diabetes, so that finally the ratio of diabetes among ministers replying was one in forty-four, but of all those investigated was five or one for each 106 ministers, if it is assumed that we had reports for each one of the ministers in the state. The ages of the ministers I do not know.

TABLE 8.—*Present Age of Diabetic Persons in Arizona*

	Males					Females					
	Mexicans	Indians	Whites, Including Jews	Negroes	Others	Mexicans	Indians	Whites, Including Jews	Negroes	Others	Total Male and Female
Under 14	0	1	11	0	0	1	0	9	0	0	22
15-24	1	1	23	1	0	3	0	22	0	0	51
25-34	1	4	24	0	1	3	8	17	1	0	59
35-44	4	10	33	1	0	8	6	30	3	0	95
45-54	8	13	52	2	2	22	6	60	2	1	168
55-64	9	8	54	2	3	15	5	64	4	0	164
65-74	2	2	46	1	0	5	1	57	3	0	117
75+	0	1	13	0	0	1	0	9	0	0	24
Totals	25	40	256	7	6	58	26	268	13	1	700*

* Plus fifty-five incomplete cases (thirty-one females and twenty-four males).

DIABETES AMONG PRISONERS

The investigation of diabetes among the Indians in Arizona was handicapped because of their inaccessibility. The density of population on the Navajo reservation is only about 1.5 Indians to a square mile. Even with an automobile, hunting diabetic Navajo Indians is a rather exhausting sport, and to give myself a brief respite I turned to two areas where the task would be easier and there would be no worry that any person with diabetes would escape the Benedict test. In Florence is an institution admirably adapted for the purpose, and the state prison there furnished me with some 800 subjects. My preliminary inquiry was disappointing, but the superintendent and the prison physician were so cooperative that now I have the privilege of reporting that in the state prison at Florence where one diabetic individual was expected by National Health Survey tabulations, three were found, a higher percentage than on Riker's Island in New York. Just why diabetes appears more frequently among prisoners in Arizona than in New York I cannot say. At any rate I can report that the blood sugar tests of the three diabetic prisoners, as made at the Phoenix Pathological Laboratory, showed 342 mg., 458 mg. and 368 mg. respectively. The ages of the diabetic prisoners ran true to form. The average age for the diabetic prisoners was 46.6 years. Furthermore, obesity ruled among the diabetic in the Arizona State Prison just as it does in Boston. The average weight for all the prisoners was 152 pounds (69 Kg.), but the average weight of the diabetic prisoners was 194 pounds (88 Kg.). If prisoners weigh so much in Arizona, the question arises as to what the weights are for citizens of Arizona. It would be desirable to secure weights of Indians, particularly the Navajos and Pimas.

DIABETES AMONG THE INSANE

The state mental hospital in Phoenix furnished another group where one could be sure that tests for diabetes were performed on all inmates. The search for diabetic patients revealed that among an approximate thousand inmates there were fourteen with diabetes instead of the six expected. For comparison are available figures for the 26,031 mental patients in Massachusetts, among whom 219 were diabetic, or a ratio of 8 per 10,000. In other words, diabetes among the prisoners and insane in Arizona ranks high and apparently fully as high as if not higher than in similar populations in New York and Massachusetts.

TOTAL NUMBER OF DIABETIC PERSONS IN ARIZONA

The survey disclosed 755 diabetic persons in Arizona. The distribution by sex was as expected: males 358 and females 397. The age distribution was the same as that for other areas and is shown in table 8.

The crux of the situation, however, is to determine what percentage of the inhabitants of the state was covered by the survey; that I do not know, but it has been variously estimated from a low of 40 per cent for Mexicans to a high of 75 per cent for the white population. The census of 1940 will be helpful and, in fact, essential in this regard. I do not wish to enter into a detailed discussion of the various methods that could be employed to enable one to compare the morbidity incidence of Arizona for diabetes with that in other sections of the country in order to test the reliability of its mortality statistics. However, I will briefly enumerate some of them.

The number of diabetic persons in Massachusetts has been a subject of close study for many years. It was here that the first field work was done on chronic disease and therefrom certain conclusions could be drawn. Dr. Lombard and I also investigated the death certificates of 744 diabetic patients previously treated by me and found that only 62.9 per cent were so classified on the death records. Even if all had had the word "diabetes" on the death certificate only 82.5 per cent of the total number would have been thus classified by the joint causes of death. Thus the mortality from diabetes as recorded in the death records represents about two thirds of the mortality of persons with the disease and four fifths of the true mortality as measured by the joint causes of death.

TABLE 9.—*Diabetic Persons Expected and Found in Arizona*

	Cases Expected, Whole State	Cases Expected, Surveyed Population *	Cases Reported in Survey	Per Cent Ratio Cases Reported to Those Expected in Surveyed Population
Total population	1,168	537-747	755	101-141
Males	529	243-338	358	106-147
Females	639	294-409	397	97-135
White	797	382-526	565	107-148
Mexican	223	89-131	89	66-100
Indian	115	57- 77	73	95-128

* Based on estimate coverage of population in survey as follows: white: urban 60-75 per cent; rural 40-60 per cent; Mexican: 40-60 per cent; Indian: 50-66⅔ per cent; others (same as white). Mexican population known to have decreased since 1930.

During the last eleven years, beginning in 1929, in Arizona there have been 438 recorded deaths from diabetes, the low figure occurring in 1934 and the high figure in 1939. That makes an average of forty deaths a year. If it is assumed that this figure, as in Massachusetts, represents only 62.9 per cent of the deaths,

the total number of persons dying in the state with diabetes would have averaged for this period sixty-four annually. If this figure is multiplied by ten as a fair estimate for the duration of diabetes, the expected number of diabetic persons in the state would be 640, but this number is based on the whole state whereas the survey showed 755 deaths for a part of the state.

In determining the extent of the state covered, one might base it on the number of physicians reporting diabetes or no diabetes as compared with the total number of physicians, which this February in Arizona I thought, from all I could learn, to be 562. Furthermore, this proportion would be 290/562 and for the whole state the number of persons with diabetes would be raised from 755 in the survey to 1,471. Objections may be made that the physicians not reporting at all may have more or less diabetic patients than those reporting. The answer to that no one can give.

TABLE 10.—*Diabetes Death Rate (Number per Hundred Thousand Estimated Population)*

	1938 *	1937	1936	1935	1934	1933
Alabama	....	10.6	12.3	9.1	10.9	9.9
Arizona	10.7	10.0	10.8	9.9	7.6	8.0
Arkansas	....	9.2	8.9	7.9	7.8	8.1
California	....	25.3	23.7	24.4	21.7	22.9
Colorado	....	17.9	18.4	16.1	13.8	13.1
Connecticut	30.3	32.5	29.2	30.5	26.6	26.9
Delaware	....	28.4	29.3	30.5	26.9	28.8
District of Columbia	26.6	28.1	26.7	25.9	33.2	27.3
Florida	19.7	17.7	18.6	19.5	17.0	15.8
Georgia	....	12.6	12.5	12.9	12.7	11.7
Idaho	14.4	15.4	17.7	19.4	16.7	16.3
Illinois	....	27.6	29.9	26.1	28.4	26.1
Indiana	25.3	24.6	24.7	22.3	23.8	22.0
Iowa	....	22.5	24.5	20.9	24.4	22.8
Kansas	23.9	24.1	24.1	22.5	24.4	23.6
Kentucky	....	13.9	15.1	14.5	15.2	14.0
Louisiana	....	17.6	17.5	15.8	13.5	13.6
Maine	26.6	23.4	28.1	27.7	28.4	28.7
Maryland	28.6	26.3	27.5	27.1	23.8	23.7
Massachusetts	....	33.7	31.4	29.7	30.3	28.2
Michigan	....	26.2	26.8	26.0	23.7	23.5
Minnesota	26.5	24.5	26.2	22.8	23.3	21.5
Mississippi	....	12.6	12.4	11.9	11.1	11.3
Missouri	....	20.6	22.6	20.7	23.0	22.4
Montana	21.9	21.9	23.5	21.1	22.4	17.1
Nebraska	25.1	26.1	26.2	24.7	26.0	23.8
Nevada	16.8	18.8	13.0	13.1	17.3	16.7
New Hampshire	33.7	31.4	31.1	29.1	29.4	26.0
New Jersey	29.6	30.8	30.5	28.3	27.2	28.7
New Mexico	....	8.1	8.8	8.5	9.2	9.5
New York	....	36.9	35.8	32.6	32.3	31.8
North Carolina	....	11.1	11.9	10.7	11.4	11.0
North Dakota	....	17.1	18.8	18.6	19.7	20.1
Ohio	....	26.7	27.4	25.9	25.1	23.8
Oklahoma	....	12.3	14.6	12.3	12.0	10.6
Oregon	....	25.9	23.3	25.0	20.5	22.4
Pennsylvania	....	31.3	27.9	27.9	27.4	26.1
Rhode Island	41.9	42.0	33.8	33.0	33.9	35.9
South Carolina	....	11.7	11.8	12.2	11.9	11.2
South Dakota	18.5	19.1	21.7	19.1	23.0	18.9
Tennessee	....	11.4	11.6	11.7	10.9	10.7
Texas	....	12.6	12.7	11.7	11.8	11.6
Utah	20.8	18.5	20.3	17.9	17.5	13.5
Vermont	30.3	24.5	25.5	30.8	37.2	28.6
Virginia	....	17.0	16.5	16.0	17.4	15.0
Washington	24.8	23.5	24.8	23.1	21.4	22.0
West Virginia	....	15.2	14.6	14.2	12.0	12.4
Wisconsin	30.3	26.6	30.0	26.3	25.1	24.2
Wyoming	17.4	17.9	15.5	17.2	10.4	13.5

* Rates based on 1937 population; no estimate made for 1938.

The number of diabetic persons in Massachusetts has been most carefully estimated and if the number 17,500 is divided by the number of physicians practicing in Massachusetts, 7,528, the result is 2.3 diabetic patients reported by each physician. If this same method is applied to the 290 physicians reporting 755 diabetic patients, there are 2.6 per physician in Arizona.

Still another method is available, namely to assign to the state the expected number of diabetic persons based on the National Health Survey and at the same time with arbitrary allowances for coverage for the various types of population. For this special calculation I am indebted to Mr. Marks.

The calculation shows that for all groups save Mexicans, and the indications are that the Mexican population has decreased appreciably since 1930, the percentage ratio cases reported to those expected in the population surveyed met the requirements at both the lowest and the highest estimations of coverage.

Of far greater significance in my own mind than these various estimations are the following two letters of approval which I have received respectively from Dr. Lombard, and Dr. Dublin and Mr. Marks.

At the present time when the available census records are ten years old it is impossible to compute either morbidity or mortality rates with any assurance that they will be reasonably accurate. However, from a careful study of the morbidity data collected by Dr. Joslin and applying to an estimated population of both Arizona and Massachusetts the age specific diabetes morbidity rate obtained in the National Health Survey, an expected number of the cases was such that I am strongly inclined of the opinion that diabetes morbidity does not vary greatly in this country. Mortality does vary and a logical explanation of this would be that for some reason or other many individuals dying with diabetes are not so certified on their death certificates.

HERBERT L. LOMBARD, M.D., Boston.

Low recorded death rates from diabetes, as in Arizona, which you chose for your survey, must not be accepted at their face value. Factors such as age, sex and racial composition of the population, the density of population, economic status, and the number and location of doctors and hospitals all influence the recorded mortality. Thus, it is known that the mere adjustment of death rates to a common sex-age basis reduces appreciably the margin between the diabetes death rates in a state like Arizona and those which have high reported death rates. The rates in Arizona's cities are of the same order of size as those elsewhere in the country. Furthermore, your survey has shown an incidence of diabetes, based on actually reported cases, which after suitable allowance for her low proportion of old people and her high ratio of males to females, very much closer to the average for the country than is found in the mortality data. For the population of the state as a whole, and for the various groups by sex, age and race, the numbers of reported cases approximate, within reasonable limits, the numbers one would expect to find in comparison with the general prevalence of diabetes.

June 11, 1940.

LOUIS I. DUBLIN, PH.D., and HERBERT H. MARKS, New York.

CONCLUSIONS

In Arizona the reported diabetic mortality is not consistent with diabetic morbidity. A survey of persons with diabetes in the state conducted by Arizona physicians and myself, granting a reasonable allowance for the number of persons covered in the survey, makes it evident that the incidence of diabetic morbidity in Arizona is comparable to that of the National Health Survey. This held true for all groups including Jews, physicians, ministers, prisoners, the insane, males and females, the white population and the Indian population. Among the Mexican population there was a deficit, as the number of persons with diabetes found was less than the theoretical number expected, for which the explanation may be inaccuracy of population data. Final calculations based on the number of persons with diabetes in Arizona must await the completion of the 1940 census.

A diabetic survey in Arizona supports the thesis that diabetes is universal and conforms to the rule that the incidence of diabetes is highest where (1) the average age is the greatest, (2) women predominate, (3) obesity is most frequent, (4) the proportion of Jews is greatest, (5) medical supervision is closest and (6) deaths are most accurately reported.

81 Bay State Road.

PREDICTION AND PREVENTION OF PREGNANCY ACCIDENTS IN DIABETES

PRISCILLA WHITE, M.D.
AND
HAZEL HUNT, A.B.
BOSTON

Our present conception of the mechanism of the accidents in diabetic pregnancies has been the outcome, first, of our realization that adequate dietary control of diabetes and insulin therapy did not lower the fetal mortality rate and, second, our correlation of the behavior of diabetic pregnancies in relation to the balance of pregnancy hormones—chorionic gonadotropin, estrogen and progesterone.[1] We believe (1) that an abnormal rise of chorionic gonadotropin after the twentieth week to a level of 200 rat units per hundred cubic centimeters of blood predicts in the diabetic premature delivery, stillbirth and neonatal deaths, (2) that these accidents are caused by a failure of production or of metabolism of estrogen and progesterone and (3) that they are prevented by continuous substitutional estrogen and progesterone therapy in replacement doses.

These conclusions are based on an analysis of sixty-one completed diabetic pregnancies treated and studied at the George F. Baker Clinic between January 1936 and June 12, 1940. The earlier hormonal analyses were made by Dr. George Van S. Smith and Mrs. Smith in their laboratory to complete their studies in the problem of preeclamptic toxemia of pregnancy, and the later ones have been done in the laboratory of the New England Deaconess Hospital, where we have attempted to establish them on a routine as well as on a research basis.

The sixty-one patients studied fall into three groups, twenty-five whose hormonal balance was normal, twelve whose hormonal balance was abnormal and uncorrected, and twenty-four whose balance was abnormal but who received substitutional estrogen and progesterone therapy.

The clinical course and outcome of the twenty-five normal hormonal diabetic pregnancies was uneventful. None developed preeclamptic toxemia, none had premature deliveries, and fetal survival was 92 per cent. One death was due to asphyxia pallida and one to hemorrhagic disease of the newborn. Contrast this experience with the course of the twelve patients whose values were abnormal and who received no therapy. Nine of the twelve developed preeclamptic toxemia, the remaining three had premature deliveries, and fetal survival was only 42 per cent. From this small group the pattern of behavior of pathologic diabetic pregnancies was clarified to us. Maternal and fetal behavior fell into two groups. After the abnormal rise of chorionic gonadotropin either the mother had a lightning-like toxemia, usually with hydramnios and delivery of a macerated stillborn child, or without toxemia was delivered prematurely of a mature-appearing atelectatic infant dying within a few hours of birth.

Prevention of the accidents was our next problem. At the suggestion of the Smiths,[2] substitutional estrogen and progesterone therapy in replacement doses was started. Thirteen patients were given daily doses of from 150,000 to 450,000 international units of estradiol and from 10 to 40 mg. of benzoate proluton. Toxemia was controlled, premature deliveries did not occur, and fetal survival was 92 per cent. Though successful, this treatment would have been no more than a physiologic curiosity because of prohibitive cost but was supplied for these investigations through the courtesy of a manufacturer. Our next problem was the substitution of something inexpensive and preferably oral for estradiol benzoate and proluton. Through a grant from the National Research Council this study has been made possible, and eleven patients have been treated with oral stilbestrol in doses of 40 to 120 mg. daily and pregnolinine 10 to 40 mg. daily, the stilbestrol being supplied through the courtesy of another manufacturer.

The clinical results are comparable: Toxemias were controlled, no markedly premature deliveries occurred and, barring one case of fatal erythroblastosis, the third erythroblastosic infant of this mother, the fetal survival was excellent, 90 per cent. The one failure had perfectly controlled diabetes but imperfectly controlled hormonal balance, developed toxemia and delivered normally a typical gigantic macerated fetus.

Our present plan of treatment is oral therapy, but if the gonad stimulating factor called "prolan" is not falling to satisfactory levels after two weeks' adequate trial with stilbestrol in doses up to 120 mg. daily, stilbestrol given intramuscularly up to 50 mg. is substituted for the oral preparation. Among sixteen patients who have been or are being treated with massive doses of stilbestrol, no side reactions have occurred and no toxicity measured by bilirubin excretion tests has been observed.

Let us compare the fetal survival in our three groups: 92 per cent when the hormonal balance was normal, 42 per cent when the balance was abnormal and uncorrected and 87 per cent, including the case of erythroblastosis, when the abnormal balance was corrected.

The high level of late fetal mortality, namely 33 per cent, which was our yearly rate until 1938, is the one reported among diabetic clinics througout the world. Obstetric hospitals have reported lower rates, we believe, because of the difference in patient clientele. Obstetric hospitals see many short duration cases with onset of diabetes in pregnancy, transitory hyperglycemia and glycosuria—patients whose clinical course and endocrine balance is different from that of chronically progressive diabetes. Diabetic clinics see more cases of diabetes of long duration with pregnancy incidental to the disease. Since our own practice is consultative, we refer back the borderline and short duration cases and deliberately select potentially abnormal cases. But the value of this presentation lies in this very fact—the obstetrician will see more patients of this type, for not only does one girl in 2,500 contract diabetes, but after many years' duration of the disease she will now live to the child-bearing age.

Delivery depends on clinical and hormonal behavior. Cesarean section is favored in the abnormal group, normal delivery in the normal group.

The treatment of diabetes is the simplest part of our problem. The diet must be adequate, carbohydrate liberal, from 150 to 250 Gm., protein 2 Gm. per

From the George F. Baker Clinic of the New England Deaconess Hospital, Elliott P. Joslin, medical director.

Read before the joint meeting of the Section on Obstetrics and Gynecology and the Section on Pediatrics at the Ninety-First Annual Session of the American Medical Association, New York, June 14, 1940.

1. White, Priscilla; Titus, R. S.; Joslin, E. P., and Hunt, Hazel: Am. J. M. Sc. **198**: 482 (Oct.) 1939.

2. Smith, George Van S., and Smith, Olive Watkins: Am. J. Obst. & Gynec. **39**: 405 (March) 1940.

kilogram of body weight, fat to complete the caloric prescription of 30 calories per kilogram. Medicinal minerals and vitamins are added. Insulin dosage, to avoid the pitfalls of low renal threshold, is controlled by blood rather than urinary sugars.

In a group of sixty-one patients we believe we have demonstrated that the accidents commonly seen in diabetic pregnancies are not due to imperfectly controlled diabetes but to an abnormal hormonal balance, a rise of chorionic gonadotropin, fall of estrogen and progesterone. These accidents are prevented by continuous substitutional estrogen and progesterone therapy in replacement doses. Finally, we believe that this treatment is no longer a physiologic curiosity but one well within the field of practical therapeutics.

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THE NEONATAL PROBLEM IN INFANTS OF DIABETIC MOTHERS

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Infants of mothers with diabetes mellitus show a high morbidity and mortality rate. My object in this paper is to present sixty-five consecutive infants of diabetic mothers studied during the past ten years. Such a group of infants was almost nonexistent two decades ago, before the insulin era. Women with diabetes either did not become pregnant or failed to give birth to a living child. Since the insulin era, the fecundity of the diabetic woman has greatly increased, and the juvenile diabetic patient has now reached the childbearing age. There is, therefore, an increasing number of pregnant women with diabetes mellitus and an increasing number of infants of diabetic mothers.

This group of infants has not been studied in large enough numbers to permit definite conclusions. There are sufficient data, however, to warrant certain general conceptions with regard to these infants. Miscarriages and stillbirths are most common in this group.[1] There has been a great variation in the mortality rate, and reports showing rates as high as 40 per cent have been recorded. A second conception is that these babies are unusually large and are frequently called "giant infants" at birth.[2] There is no evidence, however, to show that the skeletons of these infants are larger than normal or that these babies develop into larger types. A third conception from previous studies is that these infants are frequently born with hypertrophy of the islands of Langerhans. Recent work [3] has shown that the majority of the infants studied have this condition, although it may also be found in normal infants. A further prevalent conception is that these infants frequently present symptoms due to hypoglycemia.[4] For this reason it has been advocated that all infants of diabetic mothers be given parenteral dextrose immediately after birth. Recent observations,[5] however, have not confirmed this idea.

The material for the present study has been afforded by the clinic of Dr. Elliott P. Joslin of Boston. I myself have observed these sixty-five infants throughout the neonatal period. The care of the mothers has been uniform and has been modified only by newer concepts of diabetic treatment. One obstetrician has delivered all these babies.[6] Analgesics prior to delivery were given to some of the mothers in this series. Most of the babies have been delivered by cesarean section under spinal anesthesia without preoperative medication. There have been no maternal fatalities.

The procedure adopted for the care of these babies has been as follows: The infant is immediately drained and all material obstructing the upper respiratory passages is removed by suction. If the infant is sluggish in breathing, no mechanical effort is made to resuscitate it. The baby is placed in an incubator with controlled conditions of heat, humidity and oxygen and left in this atmosphere for at least twenty-four hours. Nothing is given by mouth during this period. If the infant's condition is satisfactory, small doses of dextrose are started on the second day. From 1 to 2 drachms (4 to 8 cc.) of 5 per cent dextrose is given at first, and this amount is increased by from 1 to 2 drachms each feeding until 1 ounce (30 cc.) is given. All precautions are taken to avoid infection. Attempts have been made to have these infants nurse, but in general this has been unsuccessful. Microdeterminations of the blood sugar are made on the baby directly after birth and every four to eight hours during the first day. If symptoms do occur the oxygen atmosphere is continued and emphasis is placed on the importance of removal of material from the upper respiratory tract. It was a routine procedure during early observations to give parenteral dextrose directly after birth regardless of the blood sugar determinations. This procedure has not been carried out recently. A careful physical examination has been made on each infant during the first day of life. Tests for syphilis have not been made on these babies but tests on the mothers have given negative results in all cases.

This series of sixty-five infants of diabetic mothers has been divided for the purpose of study into three groups. The first group consists of thirty-seven infants, or 57 per cent of the total, who were normal at birth and whose course during the neonatal period was uneventful. There have been included in this group a few babies who were somewhat sluggish in breathing and who had minor degrees of cyanosis but who were not considered distinctly different from a great many so-called normal babies directly after delivery. Table 1 shows that 35 per cent of these infants were born of mothers who had had diabetes for from ten to twenty years and that 78 per cent of the infants were delivered by cesarean section. In this group 86 per cent were delivered between the eighth and the ninth month of gestation. The babies varied greatly in weight but the majority weighed between 6 and 10 pounds (2,720 and 4,535 Gm.). There were many mothers in this group who showed symptoms of preeclamptic toxemia.

The second group of this series consists of sixteen infants who survived but presented definite major symptoms, which generally occurred directly after delivery. These symptoms were not uniform. The infant would generally cry well at birth and be slightly sluggish in attaining normal color but at the end of two or three hours would develop a slight respiratory grunt. This

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Read before the joint meeting of the Section on Obstetrics and Gynecology and the Section on Pediatrics at the Ninety-First Annual Session of the American Medical Association, New York, June 14, 1940.

1. Joslin, E. P.: The Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1940, p. 693.
2. Fischer, L.: Zentralbl. f. Gynäk. **59**: 249 (Feb. 2) 1935.
3. Helwig, E. B.: Hypertrophy and Hyperplasia of Islands of Langerhans in Infants Born of Diabetic Mothers, Arch. Int. Med. **65**: 221-239 (Feb.) 1940.
4. Randall, L. M., and Rynearson, E. H.: Delivery and Care of the Newborn Infant of the Diabetic Mother, J. A. M. A. **107**: 919 (Sept. 19) 1936.
5. Miller, H. C., and Ross, R. A.: Relation of Hypoglycemia to the Symptoms Observed in Infants of Diabetic Mothers, J. Pediat. **16**: 473 (April) 1940.
6. The mothers of the infants in this series were under the obstetric care of Dr. R. S. Titus and under the medical care of Dr. Priscilla White.

gradually became more accentuated, and the respirations often reached from 100 to 110 a minute. The reflexes usually became distinctly suppressed and crying could be elicited with difficulty. Jerky movements of the extremities were not infrequent and there invariably developed varying degrees of cyanosis. These symptoms usually persisted during the first twenty-four hours and rarely lasted more than two days. The baby's condition was generally improved by oxygen. Parenteral dextrose was given to a number of these infants without change in symptoms.

TABLE 1.—*Summary of Thirty-Seven Infants, Born of Diabetic Mothers, Who Presented No Major Symptoms*

	Duration of Diabetes		Delivery,	Month of Gestation			Infants' Weight, Pounds	
	1-10 Yrs.	10-20 Yrs.	Cesarean	7	8	9	4-6	6-10
Number	24	13	29	5	16	16	5	32
Per cent	65	35	78	14	43	43	14	86

Physical examination of these infants directly after birth showed no demonstrable cardiac abnormality. The respiratory murmur over the lungs was frequently suppressed and was considered to indicate a marked degree of primary atelectasis. Some of the infants showed definite edema of the extremities and face.

In this group of sixteen infants, 31 per cent of the mothers had had diabetes for a period of from ten to twenty years (table 2). About a third of the mothers showed definite signs of preeclamptic toxemia with elevation of blood pressure, edema and albuminuria. Fifty per cent of these infants were delivered by cesarean section and all were born between the eighth and the ninth month of gestation. The weights of these babies were not unusual.

The following histories are examples of infants in this group who presented major symptoms:

REPORT OF CASES

CASE 29.—A female infant was delivered by cesarean section of a woman aged 24, who had had recognized diabetes for four years. The mother had been receiving approximately 14 units of regular insulin and 34 units of protamine zinc insulin late in her pregnancy. Her diabetes and pregnancy were uncomplicated. Her catamenia had been regular. This was her first pregnancy.

Cesarean section was done because the fetus was considered exceptionally large for the estimated eighth month of gestation. The baby at birth presented the appearance of a full term, mature infant. She weighed 8 pounds 10 ounces (3,912 Gm.). The dimensions were as follows: length 51 cm., head circumference 34 cm., thorax 33 cm. The delivery was performed under spinal anesthesia without preoperative medication. The placental attachment was beneath the uterine incision. The infant was not considered unusually cyanotic at birth and cried satisfactorily. There developed soon after birth a respiratory grunt, and considerable cyanosis of the extremities persisted. Thin yellowish fluid resembling amniotic sac contents was aspirated repeatedly from the trachea and recovered by postural drainage. There developed during the first few hours extreme degrees of general cyanosis with very shallow respiratory excursions. These attacks were apparently relieved by oxygen. The baby received 65 cc. of 5 per cent dextrose by hypodermoclysis six hours after birth. After twelve hours, because of persistent cyanosis, the baby was placed in a respiratory chamber in an atmosphere of helium and oxygen. The baby had no further marked cyanotic attacks but otherwise showed no improvement. At the end of the second day there were general hypotonicity, cyanosis of the extremities, no nursing reflex and a persistent respiratory grunt. Without any change in treatment, respirations gradually decreased from 120 a minute to normal, the extremities became persistently pink and the baby cried vigorously. When about 60 hours old, the baby was taken out of the oxygen chamber and appeared essentially normal. No physical abnormalities were noted at this time and the infant's convalescence was uneventful. The baby lost 1 pound (450 Gm.) during the first four days. A solution of 5 per cent dextrose in teaspoon amounts was started after the infant was taken from the oxygen chamber.

The baby's blood sugar was 180 mg. per hundred cubic centimeters at birth, 170 mg. at 8½ hours, 160 mg. at 24 hours, 60 mg. at 32 hours and 60 mg. at 36 hours.

CASE 49.—A male infant was the first child of a mother, aged 25, who had had diabetes for fifteen years. Her disease was severe but well controlled. Her catamenia had been irregular but at the time of delivery physical examination suggested an eight months gestation. The pregnancy was uncomplicated except for a severe secondary anemia.

The baby was delivered by cesarean section under spinal anesthesia. Pentobarbital sodium 4½ grains (0.3 Gm.) was given preoperatively. The infant's birth weight was 6 pounds 6 ounces (2,892 Gm.). He reacted normally after birth. The cord blood sugar was 60 mg. per hundred cubic centimeters. Four hours after birth he became very cyanotic. Eight hours later the condition became worse, respirations were very shallow and convulsive movements of the extremities developed. The baby was considered moribund. At this time the blood sugar was 9 mg. per hundred cubic centimeters. Thirty cc. of 10 per cent dextrose solution was given by gavage and clinically there was great improvement in the patient's condition. The blood sugar rose to 30 mg. on the second day and to 80 mg. on the third day. He lost 10 ounces (283 Gm.) but showed no further symptoms. His reactions suggested an immature infant. Physical examination was negative and the future course was normal.

The mother was given insulin preoperatively and showed symptoms of insulin shock after delivery. Her blood sugar at that time was 50 mg. per hundred cubic centimeters.

CASE 1.—A male infant was born of a mother, aged 27, who had had diabetes for twenty years. She was a very small person, weighing about 100 pounds (45 Kg.), but members of her family were large and her husband was of average size. The mother's catamenia had been regular and this was her first pregnancy. She had many complications of diabetes and evidence of toxemia, with elevation of blood pressure and edema of the extremities. The latter disappeared with rest in bed and treatment with stilbestrol and pregnolinine. The baby was delivered under spinal anesthesia without preoperative medication by cesarean section about three weeks before term. The mother's dosage of insulin at this time was 22 units of regular and 32 units of protamine zinc insulin daily. There was definite hydramnios.

TABLE 2.—*Summary of Sixteen Infants, Born of Diabetic Mothers, Who Presented Major Symptoms*

	Duration of Diabetes		Delivery		Month of Gestation		Infants' Weight, Pounds	
	1-10 Yrs.	10-20 Yrs.	Cesarean	Unclassified	8	9	6-7	7-12
Number	11	5	8	8	10	6	4	12
Per cent	69	31	50	50	63	37	25	75

The infant weighed 9 pounds 14 ounces (4,480 Gm.) and cried lustily at birth. He passed meconium before complete extraction from the uterus. Considerable fluid was drained and greenish material aspirated by catheter. He remained moderately cyanotic for six hours. He had definite apnea and his respirations were irregular, shallow and rapid, increasing to 120 a minute. He was kept in an incubator in an oxygen atmosphere of from 40 to 60 per cent. He had no convulsions. At about 36 hours he was normal and his course was uneventful. He lost 11 ounces (312 Gm.). Physical examination showed no abnormalities. His head was 35 cm. in circumference, thorax 35.6 cm. and length 52 cm.

An x-ray film was taken after twenty-four hours which showed shadows typical of multiple atelectatic areas, suggestive

of inhalation of amniotic sac contents. The blood sugar at 2 hours was 100 mg. per hundred cubic centimeters, at 5 hours 120 mg., at 9 hours 140 mg., at 14 hours 140 mg. and at 23 hours 120 mg. Dextrose solution was started by mouth at 25 hours of age.

The third group of this series of infants of diabetic mothers consists of twelve infants who died during the first three days of life (table 3). The symptoms that these infants presented showed great variation, and there was no common cause for death. The first three infants of this group died of recognized conditions. In cases 32 and 38 the fetuses were nonviable, delivered spontaneously in the fourth or fifth month of gestation. The remaining seven infants of this group were delivered from one to two months prematurely. The weights of these infants, with two exceptions, were from 6 to 8 pounds (2,720 to 3,630 Gm.). These seven infants presented symptoms of anoxia and died within one to fifteen hours after birth. The symptoms of this group of infants were often similar to those observed in the second group except that they were associated with greater degrees of cyanosis and asphyxia. Dyspnea did not seem such a prominent symptom as in the previous group.

TABLE 3.—*Twelve Deaths of Infants of Diabetic Mothers*

Mothers					Infants				
					Weight				
Case	Duration of Diabetes	Medication	Delivery	Gestation	Pounds	Ounces	Duration of Life	Clinical Diagnosis	Anatomic Diagnosis
4	8 yrs.	Yes	Normal	9 mos.	6	3	40 hrs.	Erythroblastosis	Erythroblastosis
5	3 yrs.	Yes	Normal	9 mos.	7	3	72 hrs.	Hemorrhage of adrenals	No autopsy
53	1 yr.	No	Breech	9 mos.	6	12	20 hrs.	Cerebral hemorrhage	Tentorial tear, cerebral hemorrhage
32	4 yrs.	No	Normal	5 mos.	3	12	45 min.	Prematurity, asphyxia	Cause of death ?
38	4 yrs.	No	Normal	5 mos.	3	..	1 hr.	Prematurity, asphyxia	No autopsy
39	3 yrs.	Yes	Breech	7 mos.	4	4	8 hrs.	Prematurity, asphyxia	Prematurity
36	14 yrs.	Yes	Cesarean	7 mos.	6	12	1½ hrs.	Prematurity, asphyxia	Primary atelectasis, partial
40	4 yrs.	Yes	Cesarean	8 mos.	8	1	2½ hrs.	Asphyxia	Prematurity, cause of death ?
42	8½ yrs.	Yes	Cesarean	7½ mos.	6	4	10 hrs.	Prematurity, asphyxia	Aspiration of amniotic fluid
41	1 yr.	No	Low forceps	7 mos.	7	..	14 hrs.	Atelectasis, intracranial hemorrhage ?, asphyxia	Primary atelectasis
37	11 yrs.	Yes	Breech	7 mos.	4	8	15 hrs.	Prematurity, asphyxia	Primary atelectasis
17	12 yrs.	No	Cesarean	8 mos.	6	1	10½ hrs.	Asphyxia	Cause of death ?

Autopsies were performed in ten of the fatal cases and the exact cause of death was determined in two. Primary atelectasis was frequently noted. Evidence of aspiration of amniotic sac contents, hemorrhage of various organs and areas of hemopoiesis was common. Marked hyperplasia of the islands of Langerhans was noted in only one case.

The following histories are examples of infants who died:

CASES 37 and 17.—These two infants were born of the same mother in successive years and were the only pregnancies. The mother was 23 years old at the time of the first pregnancy and had had diabetes for eleven years. She was receiving 28 units of protamine zinc and 16 units of regular insulin during the second pregnancy. Her catamenia had been regular. Her first pregnancy was not associated with the usual signs of toxemia but before the birth of the second baby she had slight edema. The first baby was delivered by breech extraction under nitrous oxide and oxygen anesthesia two months before term. The mother received pentobarbital sodium 4½ grains (0.3 Gm.) and scopolamine 1/150 grain (0.0004 Gm.) about four hours before delivery. The second baby was delivered under spinal anesthesia without preoperative medication shortly after the eighth month of gestation.

The first baby, a girl, weighed 4 pounds 8 ounces (2,040 Gm.) and was cyanotic and atonic at birth, with suppression of all reflexes. The general appearance was that of a small, immature infant. She was placed in an incubator with a mixture of helium and 45 per cent oxygen, which relieved the cyanosis temporarily. During the next five hours severe attacks of cyanosis occurred. Apnea developed and this was relieved by artificial respiration and suction. Considerable fluid, suggesting amniotic sac contents, was recovered from the pharynx. She was given 50 cc. of 5 per cent dextrose by hypodermoclysis twelve hours after birth. The baby had a severe cyanotic attack three hours later and efforts to establish respiration were unsuccessful.

The cord blood sugar was 117 mg. per hundred cubic centimeters. At 4 hours the blood sugar was 90 mg. and at 12 hours 60 mg. per hundred cubic centimeters.

The clinical diagnosis was prematurity and asphyxia neonatorum. An autopsy was performed which showed primary atelectasis of the lungs, marked hemopoiesis of the liver and some hemorrhage of both adrenals. The pancreas appeared normal. No definite cause of death was determined.

The second baby, a boy, was regarded as normal at birth and weighed 6 pounds 1 ounce (2,750 Gm.). He presented no problems of resuscitation. Physical examination shortly after birth showed that he was a well developed infant with dimensions of the head and thorax somewhat below the average. There was no demonstrable pathologic condition of the heart and abdominal organs. The respiratory note was distinctly suppressed, especially over the upper lobes of the lungs and the left lower lobe. No rales were heard. The respirations were shallow and there was some thoracic retraction. General cyanosis was noted about two hours after birth, which increased but was modified somewhat by high concentrations of oxygen. Mild convulsive movements of the arms and muscles of the face developed. About four hours after birth he was given 75 cc. of 5 per cent dextrose by hypodermoclysis and 25 cc. two hours later, without a change in his condition. The cyanosis became more extreme, periods of apnea developed with increased suppression of all reflexes and the infant died about ten and one-half hours after birth.

The blood sugar determinations were 170 mg. per hundred cubic centimeters at birth, 40 mg. at 3 hours and 140 mg. at 9 hours.

The clinical diagnosis was asphyxia neonatorum. An autopsy revealed no evidence of cerebral abnormality. "The lungs were unexpanded and rubbery, noncrepitant and red throughout. Microscopically, only few alveoli were expanded. The pancreas showed moderate hypertrophy and hyperplasia of the islands of Langerhans with increase of the size of the islands and cells. The immediate cause of death was undetermined." The blood sugar level of the heart was 22 mg. per hundred cubic centimeters and of the liver 27 mg.

COMMENTS

Blood sugar determinations by the Folin-Malmros micromethod, as described by McKittrick,[7] were made on a large number of infants in this series. The purpose of these studies was to determine, if possible, any relationship between existing symptoms of infants of diabetic mothers and the blood sugar levels. Although determinations were made during the first three days in a large number of cases, only the results of the determinations during the first twelve hours are noted, as

7. McKittrick, J. B.: Serial Blood Sugar Determinations in Normal Newborn Infants, J. Pediat. **16**: 151 (Feb.) 1940.

invariably symptoms noted in this series of infants occurred during this period (table 4 and chart 1). It will be seen that the maximum blood sugar levels during the first twelve hours were unusually high, namely from 170 to 260 mg. per hundred cubic centimeters, and that

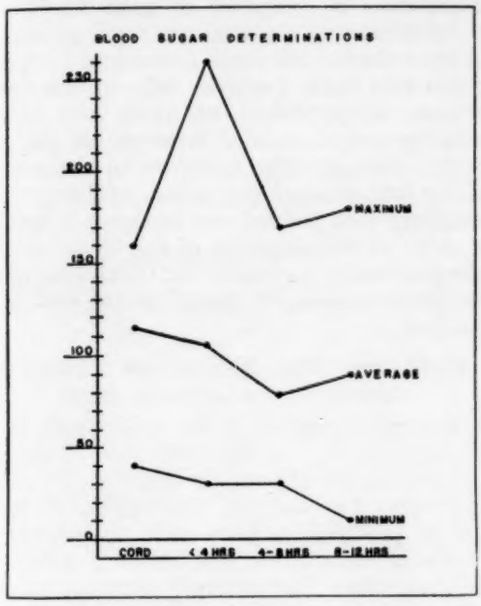

Chart 1.—Curves of maximum, average and minimum blood sugar values, based on determinations made on fifty infants born of diabetic mothers.

the average blood sugar levels during this period were much above the level usually described as normal for an infant of this age. The minimum levels were somewhat lower than the expected but, with one exception, were not unusual, especially if one compares the values given for normal immature infants during the first forty-eight hours of life, as noted by Miller and Ross.[5] The finding of 9 mg. per hundred cubic centimeters was noted in one infant (case 49), whose mother had had a large dose of insulin shortly before delivery and developed an insulin reaction after the birth of the baby. This infant's condition was greatly improved after the administration of dextrose. It is obvious from these studies that the infants in this series presenting major symptoms during the first twelve hours may have normal

TABLE 4.—*Blood Sugar Determinations—Males and Females*

	Cord	Birth to 4 Hours	4-8 Hours	8-12 Hours
Maximum	160	260	170	180
Average	113.4	104.5	79.2	89.2
Minimum	40	30	30	9
Number of determinations	23	38	34	28
Number of infants	23	31	27	25

blood sugar levels, as seen in chart 2. Furthermore, it was a common experience that parenteral administration of dextrose failed to relieve the symptoms, as illustrated in chart 2 (case 17).

It has been impossible to add accurate data in this series with regard to the possible effect of maternal diabetes on the weight of the infant. The problem is complicated by the fact that many women with diabetes have an irregular catamenia and also by the fact that 63 per cent of the infants studied were delivered by cesarean section before term. It is the distinct impression from observations at hand that the infants in this series weighed more than the average and that this is due to an excess of adipose tissue. There were fourteen babies in this series who weighed 8 pounds (3,630 Gm.) or more, and seven babies who weighed 9 pounds (4,080 Gm.) or more. Studies of these babies through the neonatal period and infancy have offered no evidence that skeletally these infants were larger than normal. There have been many instances in which infants have been delivered from one to two months prematurely and have weighed 8 pounds or more.

This study of sixty-five consecutive infants of mothers with diabetes mellitus emphasizes again the high morbidity and mortality rates in the neonatal period. In this series 43 per cent of the infants, as shown in table 5, showed clinical symptoms, and 18 per cent of the sixty-

TABLE 5.—*Outcome of Sixty-Five Infants Born of Diabetic Mothers*

Group	No. of Cases	Per Cent	Result
1	37	57	Normal course
2	16	25	Abnormal symptoms
3	12	18	Fatalities

five died. In two of the fatalities the fetuses were undoubtedly nonviable, a third had erythroblastosis, a fourth had cerebral hemorrhage with a tentorial tear and a fifth probably had hemorrhagic disease of the newborn. If these five fatalities are excluded, a corrected mortality rate would be 11 per cent. The symptoms that these infants presented cannot be regarded as specific of the infant of the diabetic mother, but there seems to be a rather typical symptom complex. It usually occurs in the first twelve hours of life and is associated with frequent and labored respirations. A moderate degree of cyanosis also is seen, but this is not extreme except in the terminal stages. Physical examination in general shows evidences of unexpanded lungs and occasional edema of the subcutaneous tissue. All reflexes are suppressed, but muscular contractions of the face and extremities are not uncommon. The cause of these symptoms cannot be explained by the use of analgesics and anesthetics, since most of the infants were delivered under spinal anesthesia without preoperative medication. The condition suggests an

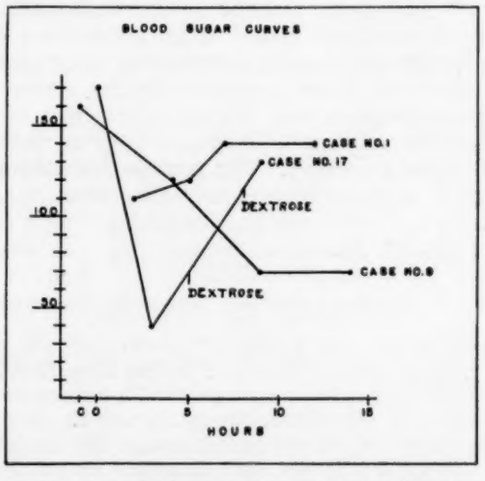

Chart 2.—Curves of blood sugar values of three infants born of diabetic mothers.

intra-uterine cause with involvement of the respiratory center. In many instances a precipitating cause has seemed to be the insufflation of amniotic sac contents.

The symptoms appear to have little relationship to the severity or duration of the mother's diabetes, as seen in table 6. Delivery by cesarean section did not appear to have an unfavorable effect on the infant, as

78 per cent showing a normal course were delivered by this method. Symptoms occurred almost twice as frequently if the infant was delivered in the eighth month of gestation, and 58 per cent of the fatal cases occurred when the infant was delivered in the seventh month. Although this study may clearly suggest the unfavorable influence of interrupting gestation before the eighth month, it should be remembered that the incidence of miscarriages and macerated fetuses among infants of diabetic mothers is not uncommon, and therefore prolonging gestation may be a greater hazard than inducing premature birth.

The study on the blood sugar levels of these infants has been disappointing as far as showing any relationship between the presenting symptoms and hypoglycemia. Experience showed early in the study the importance of maintaining a high maternal blood sugar level before delivery of the infant. It is probable that this fact modified our procedure with regard to the routine administration of parenteral dextrose to the infant of the diabetic mother directly after delivery.

TABLE 6.—*Relation of Diabetes, Type of Delivery and Period of Gestation to Viability of Fetus*

	Number of Cases	Duration of Diabetes		Delivery		Month of Gestation			Infants' Weight Under 5 Pounds
		1-10 Years	10-20 Years	Cesarean	Unclassified	7	8	9	
Normals	37	65%	35%	78%	22%	14%	43%	43%	8%
Symptoms	16	69%	31%	50%	50%	....	63%	37%	....
Fatalities	12	75%	25%	33%	67%	58%	17%	25%	33%

CONCLUSIONS

1. In a consecutive series of sixty-five infants born of diabetic mothers, 57 per cent were normal and 43 per cent presented symptoms in the neonatal period. The mortality rate was 18 per cent.

2. The symptoms presented by these infants varied greatly and were caused by many conditions. Cerebral anoxia with involvement of the respiratory center appears to be the cause of many of the symptoms presented by these infants.

3. All infants of diabetic mothers should be adequately drained and placed in an atmosphere of from 40 to 50 per cent oxygen immediately after birth.

4. Infants of diabetic mothers in this series showed high blood sugar levels. Hypoglycemia is a rare complication but may occur if insulin is given the mother shortly before delivery. The routine administration of parenteral dextrose immediately after birth is not indicated.

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ABSTRACT OF DISCUSSION

ON PAPERS OF DRS. WHITE AND HUNT AND DR. SISSON

DR. J. A. LAMPHIER, Brooklyn: At the Long Island College Hospital we have observed with considerable interest Dr. White's work regarding the relationship of toxemia in diabetic pregnancies. However, the tremendous dosages and the cost of the drugs have made it beyond our employment for practical application at our clinic. The substitution of stilbestrol for estrogen solves this problem and has answered the question I had in mind. I did not get the name of the substitution therapy for progesterone. I should like to know what drug Dr. White substitutes for progesterone, also the average dose and the average cost of this preparation.

DR. PRISCILLA WHITE, Boston: We have been substituting pregnelinolone for progesterone, and we are using less than 50 cents' worth a day. Usually we use only 10 mg. In a few cases we have had to use more than that.

TESTS OF PANCREATIC FUNCTION

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The pancreas is composed of acini lined with columnar cells; between the acini are small groups of cells termed interalveolar cell islets (islands of Langerhans). There are two main types of cells in the islands of Langerhans, distinguished as alpha and beta cells, according to special staining reactions of the granules which they contain. The functions of the acinar cells and of the beta cells of the islands of Langerhans are comparatively well defined and progress is being made in the study of the functions of the alpha cells. Tests whereby the functions of each type of cell may be studied will be reviewed, and the clinical use of such tests will be described.

TESTS FOR DISTURBANCES OF EXTERNAL SECRETION OF ACINAR CELLS

The external secretion of the acinar cells is carried by the pancreatic duct to the duodenum. This secretion is under the control of both nervous (vagal) and chemical (secretin) mechanisms. Stimulation of the vagus mechanism produces a juice rich in enzymes, while stimulation of the secretin mechanism produces a juice rich in carbonate. The external secretion of the pancreas thus serves two distinct functions: it acts as a diluting and neutralizing fluid and it provides enzymes important in digestion.

Analysis of Duodenal Content.—Among the earlier tests may be mentioned those in which the gastric content was examined after the administration of test breakfasts and those in which the urine was examined for substances liberated by digestion of capsules swallowed by the patient. These methods have only a historical interest now. Worth while clinical study of secretion of enzymes by the pancreas may be said to have begun with the description of the duodenal tube by Einhorn in 1908. Then, following the establishment of physicochemical conditions governing the activity of enzymes by Sorensen in 1909, adequate methods of chemical analysis were devised, among others by McClure and his associates [1] and by Willstätter and his associates. Many excellent data have been obtained by use of the single barrel tube similar to that described by Einhorn to remove for analysis the fasting content of the duodenum or the content of the duodenum after stimulation with various inorganic substances as well as food. However, a more accurate technic of removing the duodenal content as well as more powerful stimulants now available are requiring restudy of analysis of the duodenal content as a test of external pancreatic function.

Ågren and Lagerlöf [2] combined previously described methods [3] and used a two barrel tube; one barrel entered the stomach and the other entered the duodenum, to

From the Division of Medicine, the Mayo Clinic.

Owing to lack of space this article is abbreviated in THE JOURNAL. The complete article appears in the author's reprints.

Read before the Section on Gastro-Enterology and Proctology at the Ninety-First Annual Session of the American Medical Association, New York, June 14, 1940.

1. McClure, C. W.; Wetmore, A. S., and Reynolds, Lawrence: Physical Characters and Enzymic Activities of Duodenal Contents During Gastric Digestion in Normal Young Men, J. A. M. A. **77**: 1468-1469 (Nov. 5) 1921.

2. Agren, Gunnar, and Lagerlöf, Henrik: The Pancreatic Secretion in Man After Intravenous Administration of Secretin, Acta med. Scandinav. **90**: 1-29, 1936.

3. Lim, R. K. S.; Matheson, A. R., and Schlapp, W.: An Improved Method for Investigating the Secretory Function of the Stomach and Duodenum in the Human Subject, Quart. J. Exper. Physiol. **13**: 333-345, 1922-1923.

remove continuously and separately the gastric and duodenal contents under negative pressure. This technic has eliminated two variables acting on the external pancreatic secretion: first, the intermittent and uncontrolled stimulation of the secretin mechanisms by the entrance of acid gastric content into the duodenum and, second, the diluting effect of the gastric content. It has permitted the quantitative removal of the duodenal content, fractionation of the content as desired and, finally, calculation of the total enzyme activity per unit of time as well as the concentration for each sample. These accomplishments were impossible when the single tube was used. Moreover, the administration parenterally of potent stimulants has insured responses approaching a maximum. Two types of stimulants have been used, one purified secretin and the other those drugs which stimulate the vagus mechanism; each gives characteristic types of secretion and makes possible the selective study of the two functions of external secretion of the pancreas.

Technic of Removal of Duodenal Content with the Double Barrel Gastroduodenal Tube: After a fast of twelve hours a two barrel gastroduodenal tube is introduced into the duodenum. The structure of the tube is diagrammatically shown in figure 1. It is to be noticed that a length of tubing without perforations lies between the perforations in the stomach and those in the duodenum. When the tube is in the correct position that particular portion of the tube not perforated occupies the pyloric portion of the stomach and duodenum. That the tube occupies the correct position is determined by roentgenologic examination of the abdomen. A negative pressure of from 25 to 40 mm. of mercury has been found to be sufficient to prevent to a great extent overflow of gastric juice into the duodenum and for the collection of the duodenal content.

A half reclining position for the patient has been found satisfactory. At the clinic it has been our practice to fractionate the duodenal content into four periods of ten minutes each before stimulation and into four periods of ten minutes each and two periods of twenty minutes each after stimulation.

Secretin as a Stimulant: Physiologists, no doubt, have looked forward to the development of a test of pancreatic function using secretin as a stimulant, since its discovery by Bayliss and Starling in 1902. Although secretin was administered intravenously to a few patients as early as 1926,[4] it was not until 1934 [5] and 1936 [6] that extensive studies of external pancreatic function were carried out. In most of these studies the single barrel duodenal tube was used to remove the duodenal content. Ägren and Lagerlöf, however, employed the double barrel duodenal tube and reported more results in 1936 that seemed to picture more accurately the type of secretory response to secretin. Their results have been confirmed by Diamond and his associates [7] and by Osterberg and me.[8]

4. Chiray; Salmon, A. R., and Mercier, A.: Action de la sécrétine purifiée sur la sécrétion externe du pancréas de l'homme (note préliminaire), Bull. et mém. Soc. méd. d. hôp. de Paris **50:** 1417-1426 (July 30) 1926.

5. Voegtlin, W. L.; Greengard, H., and Ivy, A. C.: The Response of the Canine and Human Pancreas to Secretin, Am. J. Physiol. **110:** 198-224 (Nov.) 1934.

6. Chiray, M., and Bolgert, M.: Mesures de la sécrétion pancréatique externe en clinique par l'épreuve à la sécrétine purifiée, Nutrition **6:** 223-230, 1936.

7. Diamond, J. S.; Siegel, S. A.; Gall, M. B., and Karlen, S.: The Use of Secretin as a Clinical Test of Pancreatic Function, Am. J. Digest. Dis. & Nutrition **6:** 366-372 (Aug.) 1939.

8. Comfort, M. W., and Osterberg, A. E.: A Comparative Study of Pancreatic Secretion in Man Following Stimulation with Secretin and Mecholyl Chloride, Arch. Int. Med. **66:** 688-706 (Sept.) 1940.

The effect of secretin administered intravenously is noticeable within a short period of time, usually in a minute. Normal biliary color of the duodenal content rapidly becomes less marked and in many instances a clear, almost colorless secretion is obtained, provided the gallbladder is functioning. The yellowish color of the duodenal content reappears after a short time. In normal persons following stimulation with secretin the volume of duodenal content increased markedly and rapidly, usually reaching its peak within the first ten minute period. The hydrogen ion concentration usually increased one unit and reached a value of 8 or more. The carbonate content increased, roughly paralleling the behavior of the volume. The concentration of enzymes in the juice declined, reaching its low point in the second ten minute period. The total value for each enzyme per unit of time was increased but the increase was almost entirely limited to the first ten minute period,

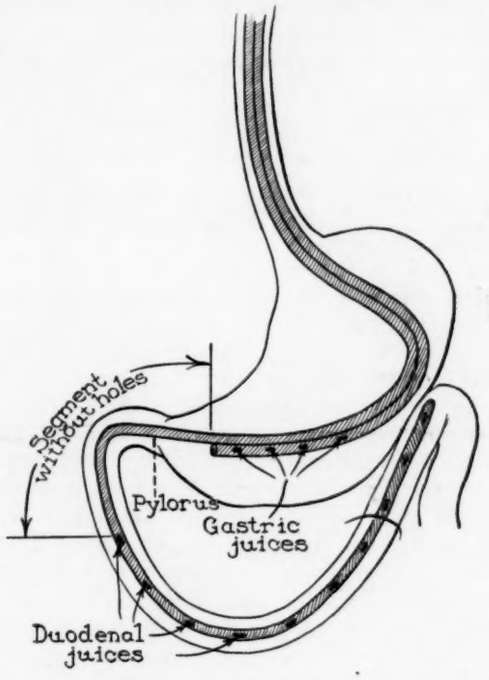

Fig. 1.—Double barrel gastroduodenal tube; one barrel ends in the stomach, the other in the duodenum.

particularly in the case of amylase and trypsin. The increase in total values appears to be due to a washing out of preformed enzymes and not due to any effect of secretin on the formation of enzymes.

The volume, alkalinity, concentration and total excretion of enzymes may be used to detect pancreatic dysfunction, as illustrated in the following case of chronic pancreatitis:

A youth aged 18 years, who registered at the clinic Dec. 12, 1938, had noted a beginning of chronic epigastric soreness, fulness after eating and two or three soft or watery stools daily in June 1937. In December 1937 a severe attack of midepigastric pain extending to the dorsal region required the administration of morphine for relief. Five additional severe attacks had occurred since that time, the last one in September 1938, but three or four mild attacks had occurred weekly. On physical examination slight tenderness in the epigastrium was the only abnormality found. Urinalysis did not disclose glycosuria and the concentration of sugar in the blood was within normal limits but the test for tolerance for dextrose showed a diabetic curve. Hemoglobinemia was present. Leukocytes numbered 15,600 per cubic millimeter, and 81 per cent were neutrophils. The lipolytic activity in terms of twentieth-normal

sodium hydroxide per cubic centimeter of serum was 2.5 cc. and the amylolytic activity in terms of units was 530. A diagnosis of chronic pancreatitis was made and confirmed at exploration in May 1939.

A test of function of external pancreatic secretion using purified secretin intravenously as a stimulant was performed. Figures 2, 3 and 4, in which the values

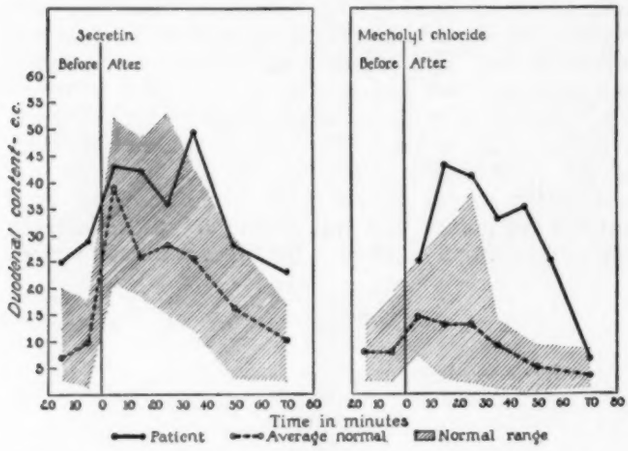

Fig. 2.—Large volume of duodenal content recovered per unit of time from a patient with chronic pancreatitis, after stimulation with secretin and with acetyl beta-methylcholine chloride, contrasted with the volumes obtained from normal persons.

obtained in this case are contrasted with the extremes as well as the means obtained in normal persons, demonstrate a hypersecretion of the pancreatic juice (fig. 2), a normal increase in values for hydrogen ion concentration but a marked hyposecretion of amylase. The values for concentration of amylase did not exhibit the typical decrease in concentration consistently seen in the second ten minute period (fig. 3) nor did the total values for amylase exhibit the usual marked increase during the first ten minute period (fig. 4). There was, in contrast, a hypersecretion of trypsin and lipase. Ägren, Lagerlöf and Berglund [9] have called attention to the frequency with which pancreatic injury causes a marked reduction in secretion of amylase without interfering with the secretion of fluid, bicarbonate or trypsin and suggested that this represents the mildest form of injury in pancreatitis. Chiray and Bolgert [6] recognized both a dissociated trypsin and a lipolytic insufficiency. In those cases in which obstruction of the pancreatic duct or destruction of pancreatic tissue occurs, as in cases of carcinoma or fibrosis of the pancreas, there is a decrease in the volume of secretion and the secretion of all the enzymes may be affected in proportion to the destruction of tissue and the degree of obstruction of the duct. Secretin used as a stimulant of pancreatic secretion should prevent the occurrence of false low total values and should disclose the more marked disturbances of pancreatic secretion as well as dissociated disturbances of secretion of fluid, alkali and the three enzymes. However, inspection of figures 3, 4 and 5 shows that mild reduction of values will not become apparent because of the variations in normal values among normal persons. While the number of published reports of tests in proved pathologic states of the pancreas is relatively small, these as well as my own experiences with the test leave little doubt in my own mind concerning the value of secretin for clinical study of the secretion of fluid, carbonate and enzymes by the acinar cells.

Drugs Which Stimulate the Vagus Mechanism: Pilocarpine, acetylcholine, acetyl beta-methylcholine chloride, physostigmine and prostigmine have all been used to stimulate pancreatic secretion. These drugs produce a secretion rich in enzymes and in this respect their action is similar to that of stimulation of the vagus nerve in animals. Osterberg and I [8] have used the two barrel gastroduodenal tube, continuous suction and acetyl beta-methylcholine chloride administered subcutaneously in doses of 15 mg. to obtain a picture of the type of secretory response obtained. Following stimulation with mecholyl chloride (acetyl beta-methylcholine chloride) a small increase in volume occurs; there is no significant change in the hydrogen ion concentration but there is an increase in the concentration of enzymes which is prolonged in duration. The total values for the several enzymes per unit of time increase for thirty minutes or longer and appear to be due to an actual increase in the secretory output of enzymes. Contrasting effects of secretin and mecholyl chloride are well illustrated in figures 2, 3 and 4, which show the extremes as well as the means for the several values obtained from normal persons.

In the case of pancreatitis already presented in abstract form, external pancreatic secretion was also studied after stimulation with mecholyl chloride. Analysis of duodenal content after administration of this drug demonstrated a hypersecretion of fluid (fig. 2), a marked insufficiency of secretion of amylase (figs. 3 and 4) but a hypersecretion of trypsin and lipase, as was the case after secretin. The same dissociation of enzymatic insufficiency that occurred after stimulation with secretin is likewise seen when using mecholyl chloride as a stimulant. A generalized reduction below the normal range of values for volume of fluid and of enzymes occurs after stimulation with mecholyl chloride in cases

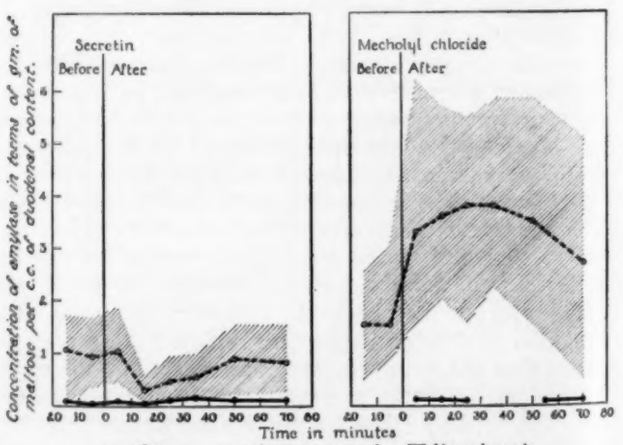

Fig. 3.—Low concentration of amylase in the duodenal content recovered per unit of time from a patient with chronic pancreatitis, after stimulation with secretin and with acetyl beta-methylcholine chloride, contrasted with the concentrations obtained in the duodenal contents recovered from normal persons.

of obstruction of the pancreatic duct and in cases of destruction of the acinar cells. Diminution of concentration as well as in total output of enzymes may give some inkling of pancreatic insufficiency. Drugs of this group and particularly mecholyl chloride should be valuable in the study of secretion of enzymes but are of

9. Ägren, Gunnar; Lagerlöf, Henrik, and Berglund, Hilding: The Secretin Test of Pancreatic Function in the Diagnosis of Pancreatic Disease, Acta med. Scandinav. **90**: 224-271, 1936.

no value in studying secretions of carbonates. Foods are distinctly less powerful stimulants of pancreatic secretion than are either secretin or mecholyl chloride.

Analysis of Stools for Enzymes.—Amylase and trypsin are normally present in the feces. Lipase usually cannot be detected. Wolfer and Christian[10] have pointed out that the amylase in the stools varies from day to day depending on the intake of food, and if the test is to be used clinically it can be effective only if the patients are placed on a uniform quantitative and qualitative diet. Even when using twenty-four hour specimens there is no constant relation between the amounts of amylase either of patients on the same diet or of the same persons from day to day, although the weekly totals approximate one another closely. Decreased values for fecal amylase occur in cases of obstruction to the duct and in extensive disease of the pancreas.[10a] Wolfer and Christian do not feel that mild involvement of the pancreas can be confirmed by determinations of fecal amylase.

Examination of the stools for enzymes has not proved to be a popular method for study of external pancreatic function for obvious reasons.

Analysis of Stools for Undigested and Unabsorbed Food.—Many observations have shown that all foodstuffs are lost in excess in the presence of pancreatic disease and have led to the gross and microscopic examination of the stools and chemical examination of the stools for undigested foods as aids in the diagnosis of chronic pancreatic disease.

Gross Appearance of Feces: The excessive loss of fat in the stools lends the characteristic appearance to the stools of pancreatic disease. Fat may be lost in the form of neutral fat, fatty acids or soap. A fatty stool may be glistening white or gray. Fat may appear as liquid fat or as masses of fat resembling butter. Fatty crystals may give the feces the appearance of aluminum paint. According to Thaysen,[11] the only form of steatorrhea which is characteristic of pancreatic disease is that in which liquid fat or masses of fat appear in the stools.

Microscopic Examination of Feces: A description of the microscopic method of examination may be found in any standard textbook on laboratory diagnosis. An excess of all food remnants may appear in the feces from excessive ingestion as well as from deficient digestion and absorption. For this reason it is preferable to carry out microscopic examinations of the stools only when patients are receiving a standard test diet, such as that of Schmidt. It is doubtful that finding microscopically any foodstuff in excessive amounts is diagnostic of pancreatic disease, as such tests of necessity must be qualitative. The finding of striated muscle fibers in excess possibly has more significance than the finding of starch granules and fat in excess, but it is best to let such observations serve as an indication for more specific tests of pancreatic function and not depend on them to diagnose the cause of the loss of food.

Chemical Analysis of Feces: In carrying out chemical analysis of the stools, the patient is placed on a standard diet such as that of Schmidt. In persons with normal digestive apparatus, digestion and absorption is fairly complete; the values for nitrogen, carbohydrate and fat in the stools seldom exceed 10 per cent of the values for nitrogen, carbohydrate and fat in the ingested food but vary somewhat with the digestibility of the food eaten. All foods are lost in excess when extensive destruction of the acinar cells of the pancreas has occurred.

Thaysen's review of the percentages of various foods lost in the feces in his own cases and in those recorded in the literature leads to the conclusion that such determinations would possibly be of limited value in distinguishing between pancreatic disease and diseases that affect intestinal absorption.

TESTS FOR DISTURBANCES OF THE "INTERNAL" SECRETION OF ACINAR CELLS

The enzymes lipase and amylase normally are active to a slight degree in the blood stream. Tryptic activity in the blood stream is said to be absent in normal persons but this enzyme has not been studied widely. Satisfactory evidence that the enzymes lipase and amylase arise partly in the pancreas may be cited; this may mean that they are in part at least an internal secretion of the pancreas, but it is not known whether they enter the blood stream directly from the acinar cells or indirectly from the gastrointestinal tract. Nevertheless, classification of values for enzymes in serum and urine as tests of internal secretion of the acinar cells is open to criticism; however, it is convenient to do so and serves to emphasize that the increased content of enzyme in the serum and urine in the presence of benign and malignant lesions of the pancreas originates in the acinar cells of the pancreas.

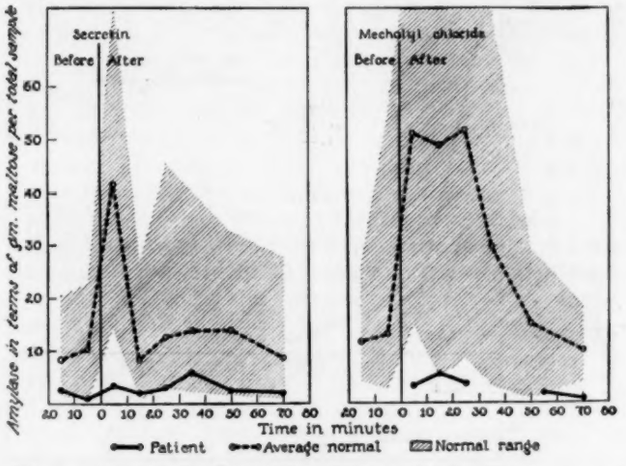

Fig. 4.—Total amount of amylase in the duodenal content recovered per unit of time from a patient with chronic pancreatitis, after stimulation with secretin and with acetyl beta-methylcholine chloride, contrasted with the total amount obtained in the duodenal contents recovered from normal persons.

The factors which maintain the normal concentration of enzymes in the serum in health are not well understood. It is believed that the liver plays a role[14] and that the anterior lobe of the pituitary gland,[15] the thy-

10. Wolfer, J. A., and Christian, L. W.: Pancreatic Function Tests with Special Reference to the Quantitative Determination of Fecal Amylase, Arch. Surg. **17**: 899-917 (Dec.) 1928.

10a. McClure, C. W., and Pratt, J. H.: A Study of the Diastatic Activity of Urine and Feces with Special Reference to Diseases of the Pancreas, Arch. Int. Med. **19**: 568-592 (April) 1917.

11. Thaysen, T. E. H.: Ueber Fettdiarrhöen, Acta med. Scandinav. **64**: 292-400, 1926. On Steatorrhoea, ibid. (supp.) **16**: 384-396, 1926; Pancreatogenous Fatty Diarrhea: Report of Case, Arch. Int. Med. **42**: 352-367 (Sept.) 1928.

14. Crandall, L. A., Jr., and Cherry, I. S.: The Regulation of Blood Lipase and Diastase by the Liver, Am. J. Physiol. **97**: 515-516 (June) 1931. Somogyi, Michael: Blood Diastase as an Indicator of Liver Function, Proc. Soc. Exper. Biol. & Med. **32**: 538-540 (Dec.) 1934.

15. Cope, O., and others: Endocrine Function and Amylase Activity: Further Observations of Blood Serum Amylase Activity in Relation to Pituitary, Pancreas and Thyroid Function in Dog and Rabbit, Endocrinology **25**: 248-256 (Aug.) 1939.

roid gland [16] and the adrenal gland [17] exert some influence. The elevated values for enzymes which occur experimentally and clinically in inflammatory disease of the pancreas and in experimental and clinical obstruction of the pancreatic duct presumably have occurred as a result of rupture of small pancreatic canaliculi permitting entrance of pancreatic juice into the blood stream, perhaps through the lymphatic vessels, but it is also possible that irritative lesions of the acinar cells provoke a hypersecretion with increased values while destruction of the acinar cells prevents the appearance of increased values.

Determination of Values for Lipase and Amylase in the Serum.—Measurement of lipolytic and amylolytic activity can be accomplished by either physical or chemical methods. Among the methods available, those recently described by Cherry and Crandall [18] for the determination of lipolytic activity and by Somogyi [19] for the determination of amylolytic activity in the serum have been proved satisfactory. The simple titration method of Cherry and Crandall uses olive oil as the

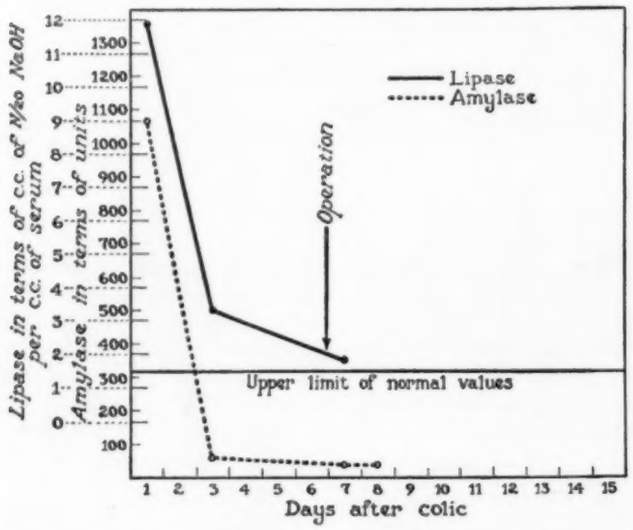
Lipase in terms of cc. of N/50 NaOH per c.c. of serum
Amylase in terms of units
Lipase
Amylase
Operation
Upper limit of normal values
Days after colic

Fig. 5.—The behavior of concentrations of lipase and of amylase in the serum in cases of acute pancreatitis; the concentration of amylase usually returns to normal levels earlier than that of lipase.

substrate and it expresses lipolytic activity in terms of cubic centimeters of twentieth-normal sodium hydroxide liberated by 1 cc. of serum. The method of Somogyi employs iodine to measure the rate of disappearance of starch, and the values are defined in terms of units. Osterberg and I [20] have found it advisable to use 1.5 cc. of twentieth-normal sodium hydroxide and 320 units as the upper limits, respectively, for lipolytic and amylolytic activity in the serum. These values are considerably higher than those originally proposed for the upper limit of values for normal persons.

Elevated values in the serum occur within a few hours after the onset of acute inflammation of the pancreas,[21] reaching a maximum within forty-eight to seventy-two hours (fig. 5). Elevated values for lipase usually return to normal within ten to fourteen days but elevations may persist over a long period of time; thus, elevated values for lipase have been obtained in every determination made over a period of months in the case of chronic pancreatitis reported herein. On the other hand, elevated values for amylase in the serum usually return to normal within a week,[22] often earlier, although elevated values following experimentally produced pancreatitis have been found to persist as long as from eight to fifteen days.[23]

Elevated values occur with great frequency in association with pancreatitis without associated disease of the biliary tract and in cases of pancreatitis secondary to disease of the biliary tract, provided the determinations are carried out within a few days after an acute attack of upper abdominal pain or during the acute stage of obstruction of the pancreatic duct. Osterberg and I [20] have laid down rigid criteria to be used in the interpretation of results in a recent analysis of our data. We expected elevated values in every case in which pancreatitis was described by the surgeon as subacute or acute, with or without fat necrosis, or as extensive (graded 3 to 4 on the basis of 4), provided determinations were carried out within seven to ten days of an acute attack of upper abdominal pain or, in other words, within the times during which elevated values could reasonably be expected. In these cases in which the pancreatitis was assumed to be active and acute, elevated values for lipase were obtained in 97 per cent of cases; a single low normal value occurred in a case of hemorrhagic pancreatitis in which a failure of values for lipase to increase was attributed to rapid and complete disintegration of the pancreas with destruction of the lipase producing tissue. More important, the condition of the pancreas was accurately indicated in 97 per cent of cases of disease of the biliary tract in which the condition of the pancreas was described by the surgeon.

The percentage accuracy of the determinations of amylase in the serum in the diagnosis of active pancreatitis was not quite so great as that of lipase, but this is probably due to the more rapid return of values for amylase to normal following an acute attack. Increased values for amylase and lipase in the serum have likewise occurred in cases of pancreatitis secondary to perforating benign and malignant lesions of the stomach and duodenum.[24] Increased values for lipase serum have been reported in 40.5 per cent of cases of carcinoma of the head of the pancreas, whereas those for amylase occur in only 8 to 22 per cent.[25] Elevated values have occurred in about 10 per cent of cases of hepatic disease, whereas elevated values for amylase

16. Bartlett, Willard Jr. (introduced by M. Somogyi): Effects upon Blood Amylase of Variations in Thyroid Activity, Proc. Soc. Exper. Biol. & Med. **36**: 843-848 (June) 1937.

17. Cope, O., and others. Endocrine Function and Amylase Activity: Changes in Activity of Blood Serum Amylase in Response to Changes in Adrenal Cortical Function in the Dog and Rabbit, Endocrinology **25**: 236-247 (Aug.) 1939.

18. Cherry, I. S., and Crandall, L. A., Jr. The Specificity of Pancreatic Lipase: Its Appearance in the Blood After Pancreatic Injury, Am. J. Physiol. **100**: 266-273 (April) 1932. Comfort, M. W., and Osterberg, A. E.: Lipase and Esterase in the Blood Serum: Their Diagnostic Value in Pancreatic Disease, J. Lab. & Clin. Med. **20**: 271-278 (Dec.) 1934.

19. Somogyi, Michael: Micromethods for the Estimation of Diastase, J. Biol. Chem. **125**: 399-414 (Sept.) 1938.

20. Comfort, M. W., and Osterberg, A. E.: The Value of Determination of the Concentration of Serum Amylase and Serum Lipase in the Diagnosis of Disease of the Pancreas, Proc. Staff Meet., Mayo Clin. **15**: 427-432 (July 3) 1940. Comfort.[26]

21. Elman, Robert: The Variations of Blood Amylase During Acute Transient Disease of the Pancreas, Ann. Surg. **105**: 379-384 (March) 1937. Comfort.[27]

22. Elman, Robert: Diagnosis and Treatment of Acute Nonhemorrhagic Pancreatitis, Am. J. Digest. Dis. & Nutrition **4**: 732-736 (Jan.) 1938.

23. McCaughan, J. M.: The Value of Estimations of the Amylase of the Blood in the Diagnosis of Suspected Pancreatic Disease; An Experimental Study and Review of the Literature, Surg., Gynec. & Obst. **59**: 598-609 (Oct.) 1934.

24. Probstein, J. G.; Wheeler, P. A., and Gray, S. H.: Perforated Peptic Ulcer: Its Differentiation from Acute Pancreatitis by Blood Diastase Determination, J. Lab. & Clin. Med. **24**: 449-452 (Feb.) 1939. Comfort.[28]

25. Wakefield, E. G.; McCaughan, J. M., and McVicar, C. S.: Amylase in the Blood in Subacute and in Chronic Pancreatic Diseases, Arch. Int. Med. **45**: 473-478 (March) 1930. Comfort.[29]

have not been reported in disease of the liver.[26] No good reason has so far been advanced for believing that these or other elevations are due to causes other than involvement of the pancreas by a disease. In short, elevated values occur in association with benign and malignant obstruction of the pancreatic duct and with inflammation of the pancreas situated primarily in the organ or involving it secondarily from diseases in the neighboring organs.

Determination of Values for Amylase in the Urine.—It is accepted that amylase in the urine is derived from the blood, that a rise in urinary diastase occurs within one to two hours after an acute attack of pancreatitis begins and shortly after the rise in blood amylase, and that the increase lasts from thirty-six to forty-eight hours and then falls suddenly and is usually normal in from three to four days. Elevations occur also during exacerbations of chronic pancreatitis. Renal damage may interfere with the excretion of amylase. Elevated values occur in cases of acute pancreatitis unassociated with disease of the biliary tract, in cases of acute pancreatitis secondary to disease of the biliary tract and duodenal ulcer penetrating into the pancreas, but rarely in cases of carcinoma of the pancreas. Wohlgemuth's original method or some modification of his method has usually been used for the determination of amylolytic values in the urine. Somogyi's method has gained favor recently.

Determinations of amylase in the urine as a test of disturbance of internal secretion of the acinar cells has been widely used for many years [27] and many conflicting opinions about its accuracy in the diagnosis of pancreatic disease have been expressed. As one reads the reports of the various investigators, the thought arises that the discouraging reports of early investigators were possibly due to ignorance of the relatively short duration of elevations of values following an acute attack and the lack of knowledge of the milder degrees of pancreatitis, and that elevated values previously thought due to cholecystitis and common duct stone were probably for the most part due to pancreatitis of a mild degree associated with the disease of the biliary tract, a type of pancreatic inflammation not widely recognized at the time when the studies were made.

It may be accepted, for the present, that elevated values for lipase and amylase in the serum and for amylase in the urine usually point to disease of the pancreas; that the pancreatic disturbance may be primary in the pancreas or secondary to disease of the biliary tract, to benign or malignant disease of the stomach, to duodenal ulcer or even to stasis in the pancreas; that determinations of the concentrations of enzymes do not allow for a diagnosis of the type of pancreatic disease nor do they serve to indicate the severity of the process; that normal values do not rule out pancreatitis since normal values may be obtained when extensive destruction of the acinar cells has occurred; that clinical symptoms and clinical signs must be used in conjunction with these tests in arriving at a clinical diagnosis of the type of disease that is present in the pancreas.

The determinations both of lipase and of amylase in the serum have their own advantages. Thus, amylase determinations can be done within the hour while that for lipase requires twenty-four hours. On the other hand, elevated values for lipase are associated more frequently with malignant disease of the pancreas than are elevated values for amylase, and the elevations for lipase in acute inflammation of the gland persist for a longer period of time than do elevated values for amylase. Elevated values for lipase in association with hepatic disease sometimes may confuse the diagnosis, but this should not be the case if the elevations in the value for this enzyme are always interpreted in the light of historical, clinical and other laboratory data.

TESTS FOR DISTURBANCES OF INTERNAL SECRETION OF ISLANDS OF LANGERHANS

Disturbed Secretion of the Hormone of Carbohydrate Metabolism.—The hormone insulin, concerned in carbohydrate metabolism, is probably secreted by the beta cells of the islands of Langerhans, and tests for disturbance of its secretion in common use in the diagnosis of diabetes mellitus may also be used in the study of disturbances of this secretion in the presence of other diseases of the pancreas. Glycosuria has been reported in from 5 to 20 per cent of cases of acute pancreatitis [28] and occurred more frequently in the severe cases. Hyperglycemia has been encountered in 50 per cent or more of the cases of acute pancreatitis [29] and occurred more frequently in pancreatic necrosis than in acute pancreatic edema. Bernhard [30] has expressed the opinion that the test for dextrose tolerance will disclose a disturbance of carbohydrate metabolism in a high percentage of cases of acute pancreatic disease in which glycosuria and hyperglycemia are absent. He also has said that the test for dextrose tolerance discloses mild disturbance of carbohydrate metabolism in the presence of pancreatic edema and discloses severe disturbances in cases of pancreatic necrosis. The test thus serves to distinguish between the two types of acute pancreatic disease. From these reports it would appear that, if preexisting diabetes can be excluded, glycosuria, hyperglycemia and disturbed tolerance for dextrose should point definitely to pancreatic inflammation if found during an attack of upper abdominal pain. However, in view of the readiness with which glycosuria, disturbances of concentrations of sugar in the blood and disturbances of tolerance for dextrose occur in association with infections, in attacks of cholecystitis and even in coronary thrombosis,[31] fasting concentrations of sugar in the blood (less than from 175 to 200 mg. per hundred cubic centimeters) and tests showing disturbance of tolerance for dextrose should be interpreted with extreme conservatism.

Tests for Disturbed Secretion of the Hormone Concerned in the Metabolism of Fat.—A depancreatized dog maintained on a balanced diet and insulin eventu-

26. Comfort, M. W.: Serum Lipase: Its Diagnostic Value, Am. J. Digest. Dis. & Nutrition **3**: 817-821 (Jan.) 1937.

27. Foged, Jens: The Diagnostic Valuc of Urine Diastase, Am. J. Surg. **27**: 439-446 (March) 1935. Mushin, M.: Urinary Diastase in Acute Pancreatitis, Australian & New Zealand J. Surg. **2**: 133-140 (Oct.) 1932. Schmieden, V., and Sebening, W.: Chirurgie des Pankreas, Arch. f. klin. Chir. **148**: 319-387, 1927. McClure and Pratt.[1]

28. Beckman, T. M.: Contributions au diagnostic des pancréatites chirurgicales, Acta chir. Scandinav. (supp. 44) **78**: 1-328, 1936. Henderson, F. F., and King, E. S. A.: Acute Pancreatitis, Arch. Surg. **30**: 1049-1057 (June) 1935. Love, R. J. M.: Acute Pancreatitis: Clinical Features and Treatment, Lancet **2**: 1262-1264 (Dec. 18) 1926. McWhorter, G. L.: Acute Pancreatitis: Report of Sixty-Four Cases, Arch. Surg. **25**: 958-990 (Nov.) 1932. de Takats and Mackenzie.[29] Rosenberg.[29]

29. Rosenberg, Max: Funktionsstörungen des Inselapparates bei akuten Pankreatitis, Klin. Wchnschr. **10**: 917-920 (May 16) 1931. de Takats, Geza, and Mackenzie, W. D.: Acute Pancreatic Necrosis and Its Sequelae, Ann. Surg. **96**: 418-440 (Sept.) 1932. Brocq, P., and Varangot, J.: L'hyperglycémie dans les pancréatites aiguës: Sa valeur au point de vue du diagnostic, du pronostic et du traitement, Bull. et mém. Soc. nat. de chir. **60**: 25-32, 1934. Casberg, M. A.: Acute Pancreatic Necrosis and Acute Interstitial Pancreatitis: Treatment Without Operation: A Clinical Study of Ten Cases, Arch. Surg. **39**: 247-263 (Aug.) 1939. Trasoff, Abraham, and Scarf, Maxwell: Acute Pancreatitis: A Medical Problem, Am. J. M. Sc. **194**: 470-474 (Oct.) 1937.

30. Bernhard, F.: Der Wort von Blutzucker- und Diastasebestimmungen für die Diagnostik, Operationsindikation und Nachbehandlung der akuten Pankreaserkrankungen, Klin. Wchnschr. **9**: 1346-1351 (July 19) 1930.

31. Raab, A. P., and Rabinowitz, M. A.: Glycosuria and Hyperglycemia in Coronary Thrombosis, J. A. M. A. **106**: 1705-1708 (May 16) 1936.

ally experiences hypolipemia and marked fatty metamorphosis together with impaired function of the liver, diminished excretion of dextrose and a marked sensitivity to insulin. In 1936 Dragstedt, van Prohaska and Harms [32] presented evidence that these changes were due to a deficiency of a hitherto undescribed internal secretion manufactured by the pancreas. They suggested the name "lipocaic" for this substance, which they assumed had to do in a general way with utilization of fat and they prepared an extract of the pancreas that would reverse these changes in the liver and increase the concentration of blood fats. Ivy and Gray [33] in 1939 concluded, however, after a review of the facts pro and con, that the evidence supporting the view that lipocaic is an internal secretion of the pancreas is by no means complete but that the evidence that lipocaic is not choline and that it is effective in preventing a deposition of fat in the liver of depancreatized dogs is very convincing. The experiments of Bensley and Woerner [34] would indicate that the alpha cells of the islands of Langerhans secrete the substance concerned with fat metabolism. Reports indicate that deficiency of the secretion of the hormone dealing with metabolism of fat has been encountered in cases of pancreatitis and among diabetic patients.[35] In these cases, bromsulphalein and hippuric acid tests have disclosed disturbances of hepatic function. Changes in blood cholesterol levels have also been observed.

COMMENT

We may safely conclude that tests exist whereby the functions of the different types of cells of the pancreas may be adequately studied.

The determination of the volume of duodenal content, its p_H values, the concentration and total excretion of bicarbonate and enzymes per unit of time after stimulation of the pancreas with purified secretin and mecholyl chloride, all constitute an especially promising group of tests of external function of acinar cells and are especially useful in cases of pancreatitis after the acute phase has passed, in cases of chronic sclerosing pancreatitis and malignant disease of the pancreas.

Measurement of the values for lipase and amylase in the serum and urine is very useful for detecting functional alterations of acinar cells due to either inflammation of the gland or obstruction of the pancreatic duct.

Determination of values for sugar in the urine and in the blood and of the tolerance for dextrose supplies trustworthy information about the secretory disturbances of the islands of Langerhans in cases of pancreatitis, provided that preexisting diabetes can be excluded.

It is emphasized that these tests are tests of pancreatic function. The results of such tests do not in themselves indicate the type or the degree of the pathologic change present in the pancreas. On the contrary, the type of pancreatic disease present and its degree of severity must be decided on the basis of the history, physical conditions and the results of other laboratory examinations.

32. Dragstedt, L. R.; Van Prohaska, John, and Harms, H. P.: Observations on a Substance in Pancreas (a Fat Metabolizing Hormone) Which Permits Survival and Prevents Liver Changes in Depancreatized Dogs, Am. J. Physiol. **117**: 175-181 (Sept.) 1936.

33. Ivy, A. C., and Gray, J. S.: Application of Recent Contributions in Basic Medical Sciences to Surgical Practice, Internat. Abstr. Surg. **69**: 1-7, 1939; in Surg., Gynec. & Obst., July 1939.

34. Bensley, S. H., and Woerner, C. A.: The Effects of Continuous Intravenous Injection of an Extract of the Alpha Cells of the Guinea Pig Pancreas on the Intact Guinea Pig, Anat. Rec. **72**: 413-433 (Dec.) 1938.

35. Rosenberg, D. H.: Proved Case of Recovery from Fatty Metamorphosis of the Liver After Treatment with Lipocaic, Am. J. Digest. Dis. & Nutrition **5**: 607-613 (Nov.) 1938. Snell, A. M., and Comfort, M. W.: Hepatic Lesions Presumably Secondary to Pancreatic Lithiasis and Atrophy: Report of Two Cases, ibid. **4**: 215-218 (June) 1937.

STUDIES IN OLD AGE

IV. THE CLINICAL SIGNIFICANCE OF SALIVARY, GASTRIC AND PANCREATIC SECRETION IN THE AGED

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AND
HEINRICH NECHELES, M.D., PH.D.
CHICAGO

The digestion of the aged has received but little attention in the literature. There is, however, a common belief among the medical profession and the public that disturbances of digestion are associated with a faulty dietary, and restriction of diet and special diets have therefore been the vogue for the aged. Much of what is accepted seems to be based on fear and habit rather than on basic experimental observations.

It is also known that gastrointestinal symptoms are common in the aged while organic diseases of the gastrointestinal tract are relatively uncommon. According to Rivers,[1] indigestion is a complaint of half of the patients between the ages of 30 and 60, and Barker [2] and his associates have studied the case histories of 300 patients past 60 years of age and noted that digestive symptoms were second highest in frequency; they found that despite the high incidence of digestive symptoms in this group there were only three cases of gallbladder disease, two of ulcer of the pylorus and two of ulcer of the duodenum. It is generally recognized that, in the aged, gastrointestinal symptoms may often be due to diseases outside the alimentary tract, as for example cardiac, renal, arthritic and hematologic disease.

Digestive disturbances, however, which may result from physiologic changes in the gastrointestinal tract, accompanying the aging process, are not clearly defined.

Observations in Two Age Groups

Age			Basal Secretion: Ptyalin Concentration		Stimulated Secretion: Ptyalin				
Years	Average	Number of Subjects	Variation	Average	Volume, Cc.	Average	Variation	Average	Specific Gravity
21-31	25	12	2.4-22.2	10.15	13.6-15	14.2	2-14.3	8.2	1.004
69-100	81	27	0.19-0.48	0.303	1.5-15	5.8	0.18-0.42	0.28	1.009

We therefore undertook a study of the secretion of the aged in order to establish what is normal and also to clarify the relationship which may exist between the secretory changes in the aged and clinical symptoms.[3]

We studied the basal (fasting) secretion of saliva and the secretion of saliva after a stimulus (chewing). Chart 1 illustrates the basal secretion of salivary amylase in thirty-two persons from 12 to 60 years of age and in twenty-nine persons from 60 to 90 years of age.[4] The results in part A of chart 1 demonstrate the forma-

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From the Departments of Medicine and Gastrointestinal Research of Michael Reese Hospital.

Read before the Section on Gastro-Enterology and Proctology at the Ninety-First Annual Session of the American Medical Association, New York, June 14, 1940.

1. Rivers, A. B.: The Dangers of Treating "Indigestion" by Advertised Nostrums, Proc. Staff Meet., Mayo Clin. **13**: 87 (Feb. 9) 1938.

2. Barker, L. C., in Cowdry, E. V.: Problems of Ageing, Baltimore, Williams & Wilkins Company, 1939, p. 717.

3. Meyer, Jacob: The Management of Diseases of the Gastrointestinal Tract in the Aged, M. Clin. North America **9**: 21 (Jan.) 1940.

4. Meyer, Jacob; Spier, Ernst, and Neuwelt, Frank: Basal Secretion of Digestive Enzymes in Old Age, Arch. Int. Med. **65**: 171 (Jan.) 1940.

tion of maltose from starch (end point method) and in part B the formation of dextrin from starch by salivary amylase. The latter method shows the intermediary products of digestion of starch by saliva, and the results obtained are of importance because only part of the starch ingested is digested completely (i. e. to maltose) in the mouth and stomach. The results demonstrate that the conversion of carbohydrates by salivary amylase to maltose and dextrin is markedly depressed in the aged, and particularly the formation of dextrin. Thus the first stage of starch digestion is severely depressed while complete digestion of starch is considerably diminished. This confirms previous work [5] in which volume and ptyalin content of stimulated salivary secretion was investigated, only the Wohlgemuth method (dextrin) being used.

The values found in this work were lower than those reported before, but different groups of subjects were employed, of different stock and on different nutrition. We are therefore of the opinion that there is a marked

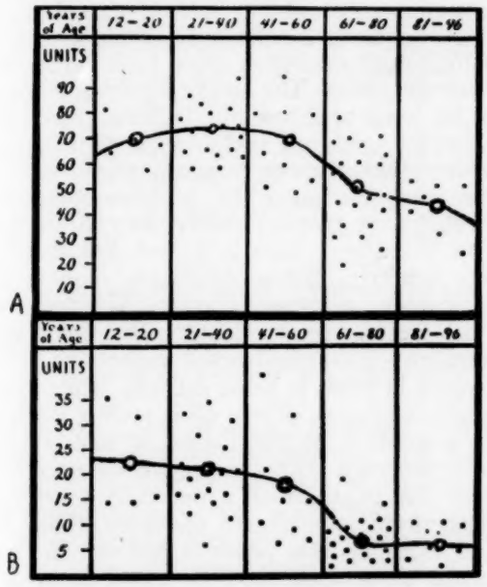

Chart 1.—*A*, salivary ptyalin estimated by the Shaw and Ross method. The enzyme activity falls little in the older age groups, although a downward trend is evident. The reaction is carried to completion, i. e. to the formation of maltose. *B*, salivary ptyalin estimated by the Wohlgemuth method. The concentration of ptyalin falls markedly about the sixtieth year of life. This reaction involves only the first step in the breakdown of starch to achroodextrin (amyloclastic action).

decrease or incomplete digestion of carbohydrates in the mouth and to a certain degree in the stomach of old people. Old people eat a considerable amount of carbohydrate foods because they are easier to chew and because in institutions for the aged carbohydrates comprise a greater portion of the diet. We expected to find evidence of incomplete carbohydrate digestion. It is of interest, however, that old people seldom complain of symptoms indicating incomplete carbohydrate digestion. These clinical observations are explained by our later investigations [6] in which we studied the pancreatic secretion of old people and discovered that stimulated pancreatic amylase is present in normal amounts while the amylase in the fasting duodenal juice is lower than in young people. This fact seems to indicate that in old people pancreatic secretion is more intermittent than in younger persons, occurring mainly after stimulation by a meal.

Our conclusion from this study is that in old people carbohydrate digestion is probably completed in the intestinal tract and that the pancreatic amylase is a substitute for the salivary amylase.

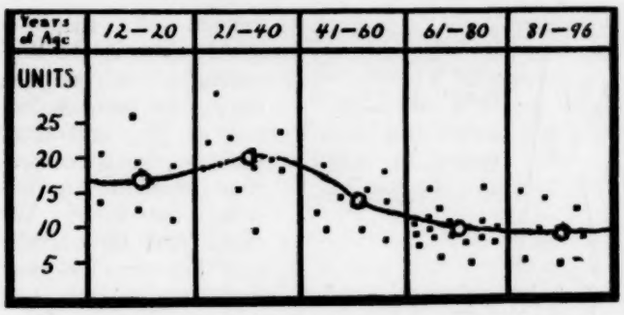

Chart 2.—Pancreatic amylase. This graph is rather similar to chart 1 *A*, except that the units are much less. It is obvious from the chart that the aged need suffer no embarrassment of carbohydrate digestion.

The dry tongue of old age may be explained by the decreased quantity of salivary secretion. The diminution of body fluids and the changes in blood chemistry may likewise be an important factor.

The tongue of the aged is often a difficult problem from a diagnostic and therapeutic aspect. It is important to differentiate the dry tongue due to metabolic disturbances and that due to such clinical entities as the anemia of the aged, achlorhydria, vitamin deficiency, Plummer Vinson's syndrome, pernicious anemia and psychogenic factors. Ivy [7] states that the atrophic changes of the mucosa of the tongue are more frequent in the elderly people with achlorhydria than in those with gastric acidity.[8] According to Hutter and Middleton [9] the atrophic changes of the tongue are more related to dietary deficiency than to achlorhydria. It is very likely that both achlorhydria and diet are involved.

It has been established by numerous investigations that the incidence of achlorhydria increases with advancing age. There is much discussion as to whether

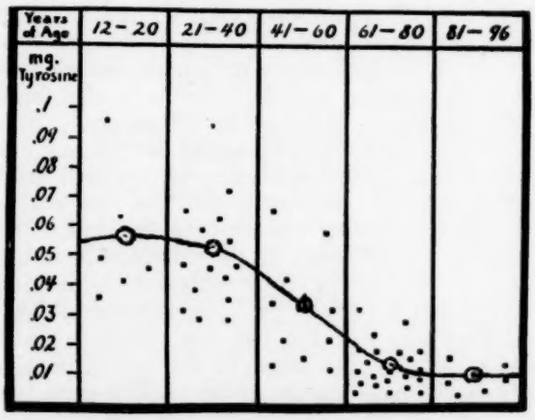

Chart 3.—Pepsin. The concentration falls sharply during the seventh decade of life and after that maintains a rather constant low value.

achlorhydria is due to a chronic gastritis, to an inherited predisposition or to a physiologic involution associated with senile atrophy. We determined the values for free

5. Meyer, Jacob; Golden, J. S.; Steiner, N., and Necheles, Heinrich: The Ptyalin Content of Human Saliva in Old Age, Am. J. Physiol. **119**: 600 (July) 1937.

6. Meyer, Jacob; Plotke, F.; Neuwelt, Frank, and Necheles, Heinrich: Studies on Old Age: A Comparison of the Secretion of the Pancreas in Old and in Young Subjects, unpublished.

7. Ivy, A. C., in Cowdry: Problems of Ageing, pp. 97, 198.

8. Davies, D. T., and James, T. G. I.: Investigation into Gastric Secretion of 100 Normal Persons Over Age of 60, Quart. J. Med. **23**: 1 (Oct.) 1930.

9. Hutter, A. M., and Middleton, W. S.: Vitamin B Deficiency and the Atrophic Tongue, J. A. M. A. **101**: 1305 (Oct. 21) 1933.

acid in the fasting gastric juice of twenty-nine patients between the ages of 60 and 96. In approximately 65 per cent of these aged subjects there was no free acid in the fasting contents, while in 35 per cent of the younger subjects there was also no free acid in the fasting contents. We likewise made determinations of the concentration of pepsin. We found a steady drop in the concentration of pepsin during the seventh decade of life, and after that age the concentration maintained a constant low value. We could find no correlation between the concentration of the acid and pepsin in the fasting gastric juice.

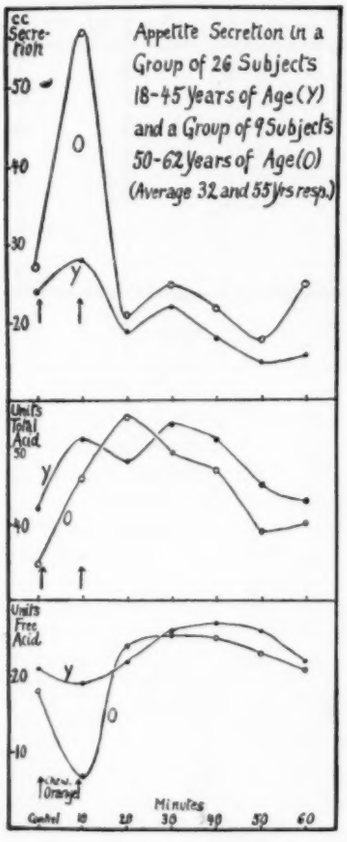

Chart 4.—Appetite secretion in a group of twenty-six subjects from 18 to 45 years of age (Y) and a group of nine subjects from 50 to 62 years of age (O), average 32 and 55 years respectively.

Chart 3 indicates the low values for pepsin in old people. It also demonstrates that in the younger group there is greater variability in the pepsin concentration than in the group of old persons, in which it is relatively constant. Osterberg, Vanzant, Alvarez and Rivers [10] made an analysis of the gastric juice of 6,200 patients and our observations parallel theirs closely in that the values for pepsin fluctuate widely in the case of young persons. These authors also found that after an Ewald meal the secretion of pepsin decreased in age as much as does the secretion of acid.

In view of the importance of psychic secretion of the stomach for appetite and digestion it is of interest to see whether this is changed in old people. The data obtained in previous work by one of us [11] were therefore regrouped and charted according to age and are presented in chart 4. It shows that the free acidity of gastric juice following the chewing of chilled orange (nothing was swallowed) drops considerably in the old people ten minutes after stimulation, while in the younger group it rises at the same interval. After that both curves rise and the two are similar. The total acidity is roughly the same in the two groups, only slightly lower in the older people. The drop in free acidity is explained by greatly increased volume of secretion in the older group ten minutes after stimulation. This shows that the drop in free acidity was due to dilution by a fluid containing combined but no free acid.

The concentration of trypsin in our study is similar to that of pancreatic amylase. The fasting duodenal contents show a decidedly lower level in the aged, while the stimulated pancreatic juice has the same concentration of trypsin in the old as in the younger group.

In spite of the low concentration of pepsin and trypsin, nothing has been written about special difficulties of old people for the digestion of proteins. It is likely that tryptic and peptic digestion in the intestine and possibly in the stomach (regurgitation) is adequate to meet the requirements of a small protein intake. We are, however, aware that there are old persons whose protein intake is fairly large who have no difficulties of digestion.

Lipase in the fasting duodenal contents and in the stimulated pancreatic secretion was distinctly lower in the old group as compared to the younger group, the difference being approximately 20 per cent. In view of the biologic reserve in all secretion this may not mean impaired digestion of fats except possibly when too much fat is ingested at one time.

The restrictions in diet, particularly restrictions of protein which are often self imposed or imposed by an overanxious or overprotective physician or family, are perhaps unwarranted in the light of our observation. With few exceptions the majority of old people select both quantity and quality of their foods which satisfy their needs and tastes. The family physician will do well to allow the aged to follow this "natural selection." It may be that the aged, just as children and animals, select foods which their organism requires.

The secretory changes which we have observed may be attributed to a gastritis rather than to the normal involution of old age. This is a most difficult problem to answer definitely. We are aware that in many people there may be no secretory change. We are likewise aware that these secretory changes may occur without any symptoms. Bloomfield noted changes in secretion with advance in years in some patients, while in others it remained unaltered. These observations likewise do not offer a solution for the changes in secretion in one group as contrasted with the apparently normal state of the secretion in others. It is necessary to make combined gastroscopic studies and secretory studies in old people to elucidate this problem further. Schindler's observations on atrophic gastritis would seem to indicate that in the aged the secretory changes are associated with a gastritis. However, our own concept is that the process is probably an involutionary change.

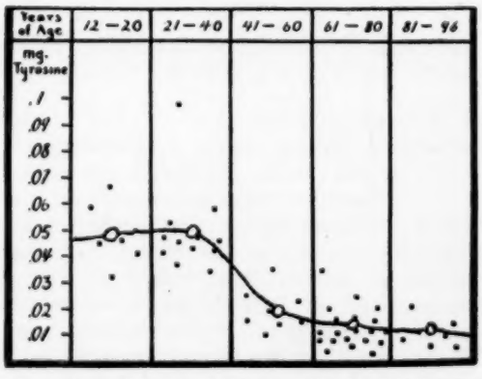

Chart 5.—Trypsin. The tryptic activity falls sharply after the fortieth year of life. The proteolytic powers of pancreatic juice bear no relation to gastric acidity.

It is possible that the quality of the food may be a factor in the secretory response. In deficiency diseases such as a vitamin B_1 deficiency there are changes in gastrointestinal secretions and motility. We therefore have made some preliminary observations on the rela-

10. Osterberg, A. E.; Vanzant, F. R.; Alvarez, W. C., and Rivers, A. B.: Studies of Pepsin in Human Gastric Juice, Am. J. Digest. Dis. & Nutrition **3**: 35 (March) 1936.

11. Necheles, Heinrich, and Maskin, M. H.: Studies on Constitution and Peptic Ulcer: I. Appetite Secretion in Normal Persons and in Ulcer Patients, Am. J. Digest. Dis. & Nutrition **3**: 90 (April) 1936.

tionship of vitamin B_1 to the achlorhydria of the aged.[12] We studied thirty-six patients between the ages of 52 and 80 who had achlorhydria to histamine and who presented no gastrointestinal symptoms; nor was there any evidence of vitamin deficiency to indicate that we were dealing with pellagra or pernicious anemia. Nine of these patients were given 15 mg. of thiamine hydrochloride hypodermically for fifteen days. No changes were observed in the free or total acidity as a result of this treatment. Nine patients were given 10 Gm. of brewers' yeast daily for a period of fourteen days and no notable change in free or total acidity was observed.

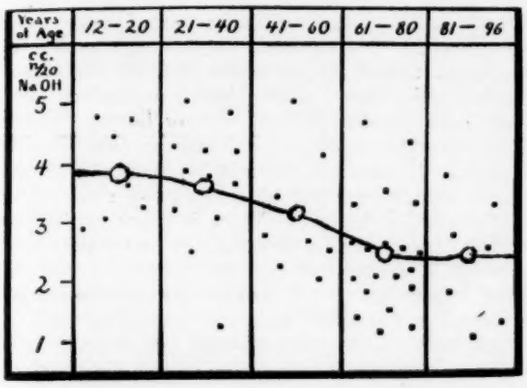

Chart 6.—Pancreatic lipase. The lipolytic activity of pancreatic juice is variable and is dependent neither on gastric acidity nor on the age of the subject.

The problem of appetite in the aged raises numerous questions. Carlson [13] quotes Sternberg as saying that the "appetite is in some way associated with the tonus of the muscles of mastication and deglutition and the absence of appetite and the nausea is due to atony of these muscles." In the aged it is common to observe changes in the tonus of the musculature of the mouth, and appetite may be absent and nausea may or may not be a complaint. Carlson states that "a certain sensation complex from the viscera and a normal state of central correlation as a necessary background for appetite. Given this background the essential in appetite is the memory process of past experience, sight, smell and taste with palatable foods. These memories are reinforced by present stimulation of these nerves by food." Visual disturances and changes which are said to occur in the taste buds and in the sense of smell in the aged may explain the absence or diminution of appetite in old people. Certainly the role of the memory process in the aged must be considered an important factor in relation to appetite. Additional factors, as the salivary and gastric secretion and the change in hunger contractions, undoubtedly play an important role in the appetite mechanism. It is important for the clinician to be familiar with the factors concerned in "appetite," particularly as it relates to old people. The older therapeutic measures such as wines, alcohol and bitters are said to be effective. Recent clinical experience shows that vitamin B is likewise of value in stimulating the appetite. While our observations indicate that vitamin B may not increase the gastric acidity in patients with achlorhydria, it may be effective in instances of lowered acidity, or again it is likely that vitamin B increases appetite by shortening the emptying time of the stomach.

12. Observations of Bernstein, Pearlman & Meyer, unpublished.
13. Carlson, A. J.: The Control of Hunger in Health and Disease, University of Chicago Press, 1916.

We wish to draw attention to the occurrence of acute peptic ulcer in the aged. It is generally believed that gastric and duodenal ulcer rarely occur in the aged and, if so, on the basis of arteriosclerosis of the gastric blood vessels. Our experience has been that ulcer is more frequent in the aged as a primary acute lesion than is generally recognized and that it is often present as a secondary disease, i. e. secondary to diseases of liver, kidney, heart or prostate. The general theory as to the genesis of ulcer presumes the presence of hyperacidity, but the relative frequency of achlorhydria or low values of acidity suggest that in the aged there may be other factors than the corrosive action of hydrochloric acid and pepsin responsible for the genesis of peptic ulcer. A gastritis in the aged as being an important factor in the etiology of ulcer is readily conceivable, because the diminution or absence of free acid permits the activity of bacteria to precipitate the ulcer process.

The frequency of perforation of peptic ulcer in the aged is also not readily explained. If the progress and activity of an ulcer are dependent on the digestive action of free hydrochloric acid and pepsin, one would expect fewer perforations because of the diminution of acid and enzymes. The occurrence of a fairly large percentage of perforations would indicate that there may be other factors which give rise to perforation in the aged.

SUMMARY

1. Gastrointestinal symptoms are common in old age, but gastrointestinal disease is relatively uncommon.

2. Old people show changes in the salivary, gastric and pancreatic secretion (except amylase), all of which are a decrease in the quantity of secretion and enzymes.

3. The diminution in the quantity of secretion apparently does not affect intestinal digestion.

4. Despite the diminution in the secretion, the secretory mechanism is capable of response under adequate stimulation.

5. Restrictions imposed on old people because of fear of inadequate digestion of carbohydrate, protein and fat do not appear warranted.

6. Acute peptic ulcer with severe complications occurs in old people in association with cardiac, renal, hepatic and prostate disease.

55 East Washington Street.

ABSTRACT OF DISCUSSION

ON PAPERS OF DR. COMFORT AND DRS. MEYER AND NECHELES

DR. JOSEPH S. DIAMOND, New York: The older methods of studying the external secretion of the pancreas presented many difficulties. The use of food as a stimulus, the admixture of gastric chyme and the lowered p_H values prevented one from obtaining accurate determinations of the functional activity of the gland. With the introduction of a purified secretin and the use of the double lumen gastroduodenal tube these difficulties have been overcome. Secretin is a potent pancreatic stimulus which is used parenterally in standard dosage. The separate collection of duodenal and gastric juices enables one to obtain a clear, uncontaminated pancreatic juice. The withdrawal of the juices under gentle suction supplies one with the total output of the secretion of the gland for a given time, for the complete quantitative study of the volume, alkalinity and the enzymes amylase, trypsin and lipase. The volume of pancreatic juice collected following the secretin injection varies between 135 and 250 cc. and is rich in bicarbonate and all the enzymes. Physiologically the secretion of the pancreas is controlled by a neurohormonal mechanism. The volume and bicarbonate are directly proportional to the hormone secretin, while the enzymes are dependent in addition to the vagal tone. When vagal stimulants

such as insulin and acetylcholine are used in conjunction with secretin the concentration of the enzymes is increased from two to three fold, while the volume and bicarbonate remain unchanged. Dr. Comfort has used mecholyl while I have used insulin, injecting 16 units intravenously one half hour before secretion. In pathologic states of the pancreas the enzymes become affected first, bicarbonate last of all. The enzymes may become dissociated so that one may be affected more than another. In severe lesions all functions are simultaneously affected. I have been working with secretin since 1938. Dr. Siegel and I have performed by now 130 tests in 104 individuals, of whom twenty-four were normal and eighty pathologic. The test has helped us to discover lesions of the pancreas in many instances in which it was least suspected. In cases of painless jaundice, with identical clinical pictures of obstructive jaundice, the test has helped us differentiate a carcinoma of the head of the pancreas from a primary lesion of the common bile duct. In acute hemorrhagic pancreatitis the test revealed a very marked depression in all the functions, showing but little recovery even as late as ten months after the operation. In a group of cases of steatorrhea we were able to differentiate the idiopathic forms from those having pancreatic disturbances.

DR. A. C. IVY, Chicago: I should like to commend Dr. Meyer and Dr. Necheles and their associates for the type of work they have been doing. The physiology of digestion of the infant and child has been placed on a sound basis by experimental and clinical investigation. In the field of geriatrics the physiology of digestion will be placed on a sound basis only by experimental and clinical investigation. Considerable information is available concerning the physiology of digestion in the infant, the child and the adult, but there is little information regarding that subject in the aged. If present population trends continue, the subject of geriatrics is likely to become as important as the subject of pediatrics is today. I should like to recommend that they continue their study on the enzymes to include studies on motor activity and then to study the coefficient of digestion of foods. The coefficient of digestion is the principal subject of interest. One should be interested not only in the enzymes that are secreted but also in the motor and the absorptive activity. By knowing the intake of protein, fat and carbohydrate and by analyzing the feces, one can determine the extent to which protein, fat and carbohydrate are being digested and absorbed. I should like to emphasize the importance of stool analysis. I have met gastro-enterologists who have forgotten the importance of stool analysis. When one performs the "new secretin" tests one should correlate the results with stool analysis. One should not be misled by the results of a study of the enzyme output of the pancreas, as occurred a number of years ago by a fractional study of the acidity of gastric contents, forgetting to study and pay close attention to the stools.

DR. EDWARD S. EMERY JR., Boston: It is a common experience to encounter elderly persons with gastrointestinal disturbances. The symptoms vary widely and are frequently similar to those accompanying organic disease in younger persons. Although it cannot be said that there are gastrointestinal symptoms of old age which are characteristic diagnostically, certain traits of behavior occur frequently enough to justify comment. Often the symptoms are intermittent, disappearing and returning for no apparent reason. Many notice a decreased appetite which their physicians attribute to a sedentary existence. Others find that their desire to eat is as good as formerly but that they are no longer able to take large meals without distress. With these patients the kind of food appears to be of less importance than the amount. Still others have a normal appetite for breakfast, whereas they have little desire for food the rest of the day. These patients find that their appetite is a good index of how well their stomach tolerates food. The "digestion" of old persons is influenced strongly by fatigue, which undoubtedly explains many of the apparent vagaries in the general behavior of their symptoms. This striking influence of fatigue would seem to be explained by the decreased enzymatic concentrations which are reported by Dr. Meyer and Dr. Necheles, because their studies suggest that the digestive ferments of the saliva and stomach are reduced in old age. Presumably the elderly cannot make secretions as rapidly as the younger person. It is interesting to know that the older pancreas responds to stimulation like the younger one. I have just reported before the American Gastro-Enterological Association the results of some studies on the enzymes of the upper jejunum made at the Peter Bent Brigham Hospital during the past year. The striking lesson from these studies is the rapidity with which the enzymes regain their normal concentration after their equilibrium has been disturbed. There was some reason to believe that the pancreas might help to readjust this disturbance. The indigestion of age is explained better by a diminution in the amounts of enzymes secreted than by the sedentary existence of these patients. Also it may explain the greater susceptibility to physical fatgue of the older digestive tract. If digestion is adequate only for breakfast, this may be due to storage of digestive elements during the night, permitting a sufficient amount for this meal but an inability to make ferments fast enough to take care of the noon and evening meals.

DR. JOHN L. KANTOR, New York: May I emphasize what Dr. Ivy has said? The clinician, in studying the work of the pancreas, must investigate the stools for his final appraisal. A. J. Carlson voiced this thought about ten years ago, and five years ago it was stressed by Dr. Pratt of Boston. The secretion of the pancreas supplies three important ferments. As far as the amylase is concerned, it must be admitted that there is no clinically effective method of studying the result of carbohydrate digestion in the stool. When it comes to the work of trypsin, that is, digestion of proteins, one can study the nitrogen, although I suppose that the effect of pepsin must also be considered. There are certain standard figures that every clinician interested in this field should try to carry in mind. First there is the total fecal fat, which should not exceed 20 per cent of the weight of the dried stool in the normal individual. Then there is the fat loss, which should not exceed from 5 to 7 per cent of the ingested fat. Finally there is the fat split, which should be about 60 to 75 per cent of the total fecal fat. To use these basic figures intelligently, it is desirable that the fat content of the diet be accurately established. Any diet the fat content of which is known can be used, or else one may employ the standard Schmidt intestinal test diet. When milk is given with this diet, the quantity of fat is about 142 Gm. daily; when cocoa is used instead of milk the daily intake of fat is about 112 Gm. A good plan is to administer this weighed diet for three or four days and to collect and analyze the stools of the last two days for their fat values.

DR. HEINRICH NECHELES, Chicago: I should like to say a few words of caution about secretin. The preparation available for intravenous injection in man deteriorates and becomes toxic on standing, as we found in assays carried out over a period of time; it is rather expensive besides. I assume that the previous speakers employed secretin Astra, the Swedish preparation. Furthermore, I believe that the secretin test cannot be interpreted easily. Secretin produces a water secretion of the pancreas containing largely bicarbonates. It seems that the increase in ferments reported by various workers is due primarily to a washing out effect and not to true secretion. It would seem better, therefore, to combine secretin with physostigmine or prostigmine as we have done, or with mecholyl, as has been reported just now. I believe even that secretin is not necessary because we get a response with mecholyl alone. I believe, however, that 15 mg. of mecholyl is a very large dose even for a normal, healthy adult, as we have experienced a number of times. Trypsin seems to be the only ferment in the small intestine that can be identified as of strictly pancreatic origin, and as long as so little is known about duodenal and upper jejunal secretions it is dangerous to conclude from a diminution of lipase and amylase that this is necessarily due to deficiency of pancreatic secretion. It might well be that a slight duodenitis will increase the output of lipase and amylase by the duodenal mucosa. Also when one collects duodenal juice following secretin one must express pancreatic secretion not by the concentration but by the total amount of enzymes. Pancreatic secretion ought to be collected quantitatively and this is extremely difficult, even with a Miller-Abbott tube. The considerable increase in the volume of psychic gastric secretion of old people surprised us. In a recent paper Bloomfield reported that he found no relation of psychic secretion to age. I recalculated his values and found that the volume increase for psychic secretion was 9 cc. for

young and 23 cc. for old persons. This confirms our results. It seems thus that in old persons the vagal secretory gastric mechanism is unimpaired and may even be more responsive than in young persons.

DR. MANDRED W. COMFORT, Rochester, Minn.: Considerable emphasis has been placed by various discussers this morning on examination of stools as a procedure of choice for studying pancreatic function. I agree that the analysis of stools for undigested and unabsorbed foodstuffs gives excellent data about the completeness of digestion, but I do not believe that the data obtained from the study of stools necessarily disclose the true status of the external secretion of the pancreas, since the small bowel may assume part of the digestive functions of the pancreas. Moreover, from the results of examination of stools for undigested and unabsorbed foodstuffs it is not often possible to distinguish disturbances of digestion secondary to pancreatic disease from those secondary to disease of absorption. Thaysen, a Copenhagen investigator, expressed the belief that the loss of more than from 35 to 40 per cent of ingested fat as neutral fat and the loss of more than 3 Gm. of nitrogen in the stools daily are the only observations from the stools which are of significance in the diagnosis of pancreatic disease. Dr. Necheles has brought up the question of reactions. I have given approximately sixty injections of secretin without a single reaction and Dr. Diamond tells me that he has not had a reaction in about 130 experiments. Acetyl-beta-methylcholine chloride (mecholyl) in doses of 15 mg. subcutaneously produces considerable discomfort and marked sweating. Patients have not objected to this reaction when they have been warned of it in advance and know what to expect. The technic of removal of the duodenal contents has been criticized. It is certainly true that possibilities of error are inherent in the method but it is the best technic that has been described so far for removal of the duodenal contents. These various methods of studying the function of the cells of the pancreas which produce the external secretion need much further use before final evaluation of their merit can be made. Ten years ago, histamine was considered by some workers to be a stimulant of gastric secretion that would produce a constant and maximal response. Today we know that histamine has not measured up to the earlier expectations. As time goes on we may find that secretin, acetyl-beta-methylcholine chloride and allied drugs have certain disadvantages; but I am sure also that they will possess considerable merit for use in the study of pancreatic secretion.

DR. JACOB MEYER, Chicago: We have been impressed for a number of years with the importance of physiologic studies such as Dr. Ivy has mentioned in order to interpret and evaluate the clinical symptomatology. Much of what he has suggested has been planned, and some of the work is in progress. We likewise have been impressed with the growing significance of old age not only as a social problem but also as a clinical problem, and gastro-enterologists particularly should be cognizant of the manifold problems which are to come to us for solution in the very near future. Dr. Aaron's observation and criticism in a sense is a fair one, but what he has said holds true for almost any type of secretory test on any individual. We recognize the variations in individuals and we must recognize the various factors which may produce these variations. We are not presenting our results as indicating any specific test. We are primarily interested in presenting what is normal for old persons. I should like to call attention to the fact that while the criticism which he has mentioned applies to the individual, statistical analysis of a group of individuals is probably the best means of determining what is normal.

Disinfection.—Destruction of the infecting organism is a logical step in preventing the spread of disease. Concurrent disinfection is the most important of the disinfection procedures. It simply represents an immediate and proper disposal of all the excretions of the patient. Terminal disinfection is essentially a question of cleanliness and is brought about by soap, water and sunshine. Terminal gaseous disinfection has been abandoned, except for destruction of insects and vermin.—Smillie, Wilson G.: Public Health Administration in the United States, New York, Macmillan Company, 1940.

SULFAPYRIDINE AND ITS SODIUM SALT

IN THE TREATMENT OF MENINGITIS DUE TO THE PNEUMOCOCCUS AND HAEMOPHILUS INFLUENZAE

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During a period of nearly thirty years we have been studying the effect of various forms of therapy in bacterial meningitis. Before the newer chemicals became available the case fatality in pneumococcic meningitis was 100 per cent in our experience and in meningitis due to Haemophilus influenzae more than 95 per cent.

The use of azosulfamide and sulfanilamide moderately improved the prognosis. In a series of fifty-three cases of pneumococcic meningitis treated by one or both of these chemicals (and specific serum when available) there were nine recoveries. In treating meningitis due to H. influenzae by means of these chemicals and specific serum the results were much less encouraging. In a series of twenty-nine cases there were only two recoveries.

The excellent results obtained with sulfapyridine in pneumonia due to the pneumococcus led us to try the use of this chemical in pneumococcic meningitis. This report is based on a series of thirty cases. The diagnosis was definitely established in each instance by culturing and typing the organisms from the spinal fluid.

Table 1 shows the distribution of the cases by sex, the wide range in age and the causative types. These items are self evident. The other data will be discussed.

Blood cultures were obtained in twenty cases. Of these, ten were positive with six deaths and ten negative with five deaths. From these small groups it would appear that the presence of bacteremia had no particular bearing on the outcome.

Consideration of the foci of infection is of the utmost importance. A definite focus in the ear or mastoid or both was found in seventeen of these thirty cases. In three others there was a strong suspicion of such a focus. In one of the cases with otitis (13) there was a petrositis. In two instances there was a fractured skull and in one a head injury with a possible fracture. While this series shows no record of definite sinus involvement, yet in view of the condition found at necropsy it seems reasonable to assume that an undiagnosed involvement of sinuses, particularly the sphenoids and ethmoids, must have been present in a number of these cases. It is highly probable also that in not a few of these cases there were multiple foci of infection.

It will be noted that in these thirty cases there were ten recoveries. In three of the fatal cases death occurred within twenty-four hours after treatment was begun.

Sulfapyridine was given orally to all of these patients. The dose varied from 4 to 8 Gm. daily, usually at intervals of four hours. Young children have as a rule an excellent tolerance, so that a daily dose of from 4 to 6 Gm. is quite safe in children more than 3 years of age. Infants may be given from 2 to 4 Gm.

From the Division of Applied Therapy, Bureau of Laboratories, Department of Health, New York City.

When the patient was unable to retain oral medication the sulfapyridine was occasionally administered by rectum in the form of an emulsion with sodium bicarbonate and acacia. The rectal dose was usually twice the oral dose.

The introduction of sodium sulfapyridine has been a distinct advantage. We have used a 2 per cent solution of this compound intraspinally, usually combined with a specific serum, in fourteen instances. The dose has been from 10 to 15 cc. after each spinal drainage. We have felt that the intrathecal use of this drug was beneficial. No untoward reactions have followed the administration in this dilution. More concentrated solutions should not be used, as there may be dangerous reactions.

The intravenous use of this compound is indicated particularly when the patients are unable to retain oral medication. In this series the sodium compound was used intravenously in only one instance. However, it was used in seven cases of meningitis due to H. influenzae and in other cases the data of which have not as yet been correlated.

The toxic effects of sulfapyridine are too well known to require detailed comment. We have encountered only mild to moderate changes in the red or white blood counts. There have been instances with evidence of renal damage, hematuria occasionally and in one case anuria associated with azotemia. It is probable that in this instance the kidney tubules were obstructed by concretions of sulfapyridine crystals, although this was not proved as no necropsy was obtained. A case which is not included in this series showed similar symptoms and at necropsy there was extensive blocking of the pelvis, calices and tubules with the sulfapyridine crystals. In this particular instance the blood sulfapyridine level was low, averaging 2 mg. per hundred cubic centimeters in spite of the ingestion of large doses of the drug. No doubt the patient was acetylating most of the sulfapyridine.

Serum has been used in addition to sulfapyridine intraspinally in most instances and occasionally intravenously. The intraspinal dose was from 10,000 to 20,000 units following each lumbar puncture. The intravenous dose varied from 100,000 to 300,000 units.

The importance of the eradication by surgery of foci of infection cannot be overemphasized. The nature of these foci has already been discussed. In our experience it is much more difficult to localize and to eradicate

TABLE 1.—*Cases of Pneumococcic Meningitis Treated with Sulfapyridine*

Case	Sex	Age, Years	Type	Blood Culture	Primary Focus	Treatment and Comment	Result
1	♂	27	4	Negative	Head injury ?	Serum, sulfapyridine orally, azosulfamide.....	Died
2	♂	3 mos.	5	Positive	Otitis, mastoiditis	Serum by vein, sulfapyridine orally, mastoidectomy.	Died
3	♀	6	4	Positive	Otitis ?	Serum, sulfapyridine orally for 2 mos.; no effect on blood; had also panophthalmitis; apparent recovery for 2 weeks and then relapse	Died
4	♂	28	18	Negative	None found	Serum by vein, sulfapyridine orally, large doses; rash, and anuria, high urea nitrogen and nonprotein nitrogen; albumin and red blood cells in urine	Died
5	♂	8	18	Negative	Otitis, mastoiditis	Mastoidectomy, sulfanilamide and azosulfamide; sulfapyridine orally	Recovered
6	♀	50	1	.....	Otitis, mastoiditis	Mastoidectomy, serum, sulfapyridine; died within 24 hours after treatment was begun	Died
7	♂	11	5	Positive	Otitis, mastoiditis	Mastoidectomy, serum by vein and intraspinally; sulfapyridine; red blood cells and sulfapyridine crystals in urine	Recovered
8	♂	13	5	Positive	Upper respiratory infection	Serum by vein, sulfapyridine.....	Recovered
9	♂	1¼	4	Positive	Otitis, brain abscess	Brain abscess drained, serum by vein and intraspinally; sulfapyridine	Recovered
10	♀	26	3	Positive	Otitis, mastoiditis	Mastoidectomy before meningitis; sulfanilamide 11 days, sulfapyridine 1 day	Died
11	♀	39	8	.....	Otitis	Sulfapyridine, serum and sodium sulfapyridine intraspinally; died within 12 hours	Died
12	♀	33	1	.....	Otitis	Sulfapyridine; in seventh month of pregnancy.....	Died
13	♂	48	3	Negative	Otitis, petrositis	Reexploration of petrous bone; serum and sodium sulfapyridine intraspinally; sulfapyridine	Recovered
14	♀	50	3	Negative	Otitis, mastoiditis	Mastoidectomy before meningitis; operation revised later; sulfapyridine, sodium sulfapyridine intraspinally; sinus thrombosis and jugular ligation	Died
15	♀	27	3	Negative	Otitis, mastoiditis	Serum intravenously and intraspinally, with sodium sulfapyridine; sulfapyridine	Died
16	♂	5½ mos.	18	.....	Otitis	Sulfapyridine	Died
17	♂	9	3	Negative	Otitis, mastoiditis	Mastoidectomy; serum and sodium sulfapyridine intraspinally; sulfapyridine	Died
18	♂	14	15	.....	Fractured skull	Sulfapyridine; sodium sulfapyridine intraspinally....	Recovered
19	♂	64	18	.....	.....	Sulfapyridine; sodium sulfapyridine intraspinally; died within 24 hours after treatment	Died
20	♂	58	3	.....	Otitis	Sulfapyridine; sodium sulfapyridine and serum intraspinally; developed pneumonia while under treatment	Died
21	♀	1½	14	Positive	.....	Serum; sulfapyridine; developed brain abscess.....	Died
22	♂	44	1	Negative	Mastoiditis	Mastoidectomy; serum; sulfapyridine.....	Recovered
23	♀	45	19	Positive	Otitis	Serum and sodium sulfapyridine intraspinally; sulfapyridine	Recovered
24	♀	46	Beyond 32	Negative	.....	Sulfapyridine; sodium sulfapyridine intraspinally; prompt improvement; medication stopped; relapsed after 17 days; same treatment resumed	Recovered
25	♀	9	Beyond 32	.....	.....	Azosulfamide 8 days; sulfapyridine.....	Died
26	♂	43	21	Positive	Fractured skull	Serum intravenously; sodium sulfapyridine and serum intraspinally two or three times; sulfapyridine; sodium sulfapyridine intravenously	Died
27	♀	62	7	.....	Otitis, mastoiditis	Mastoidectomy; serum and sodium sulfapyridine intraspinally; sulfapyridine; bronchopneumonia	Died
28	♀	8	4	.....	.....	Serum and sodium sulfapyridine intraspinally; sulfapyridine	Recovered
29	♀	1 yr. 11 mos.	4	Positive	Mastoiditis ?	Serum and sodium sulfapyridine intraspinally; serum intramuscularly; sulfapyridine	Died
30	♀	48	1	Negative	Mastoiditis ?	Serum intravenously; sulfapyridine; sodium sulfapyridine intraspinally	Died

Thirty cases; ten recoveries; three patients died within twenty-four hours after treatment was begun.

foci of infection in pneumococcic than in streptococcic meningitis. It is also our impression that multiple foci are more common in pneumococcic meningitis. We believe the difficulty in completely eradicating foci of infection is a factor in the less favorable case fatality in pneumococcic meningitis.

The discouraging results with sulfanilamide and azosulfamide in the treatment of meningitis due to H. influenzae prompted us to change to sulfapyridine and its sodium salt.

to search for possible foci of infection. In three of our patients with recovery a mastoiditis was present and a mastoidectomy was performed. Another patient with clinical mastoiditis was not operated on and died. There were two patients with ethmoiditis that were operated on and recovered. Unfortunately the material removed at operation was not cultured. One fatal case followed an operation on the palate. In one patient who recovered, the meningitis was preceded by injury and infection of the orbit.

TABLE 2.—*Cases of Haemophilus Influenzae Meningitis Treated with Sulfapyridine*

Case	Sex	Age, Years	Blood Culture	Treatment	Result	Comment
1	♀	5	.....	Serum; sulfanilamide; mastoidectomy, dural slit; sulfapyridine	Recovered	Otitis, mastoiditis
2	♀	1⅝	Positive	Serum, also intramuscularly; sulfanilamide; sulfapyridine	Died	Necropsy: diffuse meningitis; temporal lobe abscess
3	♂	16	Negative	Serum; azosulfamide; later sulfapyridine.....	Recovered	
4	♂	2½	Negative	Sulfapyridine	Recovered	Injury and infection of orbit; relapse
5	♀	2½	Negative	Sulfanilamide; sulfapyridine	Died	Followed operation on palate
6	♀	7	Positive	Serum; sulfanilamide and azosulfamide; sulfapyridine; sodium sulfapyridine intraspinally	Died	Upper respiratory infection
7	♀	2	Negative	Sulfapyridine	Recovered	Prompt recovery; one positive spinal fluid culture
8	♂	51	Negative	Sulfanilamide and azosulfamide; sulfapyridine; serum and sodium sulfapyridine intraspinally	Recovered	
9	♂	9½	Negative	Sulfapyridine; sodium sulfapyridine; serum intraspinally	Died	Began as brain abscess; operation; necropsy, large brain abscess
10	♂	2¼	Positive	Azosulfamide; sulfapyridine; rabbit serum intraspinally	Died	Upper respiratory infection; otitis
11	♀	4	Negative	Mastoidectomy; azosulfamide; sulfapyridine; serum and sodium sulfapyridine intraspinally	Recovered	X-ray examination showed mastoiditis
12	♂	1	Negative	Sulfanilamide, azosulfamide; sulfapyridine and serum intraspinally; serum in vein	Died	Necropsy: diffuse meningitis; block
13	♂	3	Negative	Sulfapyridine; sodium sulfapyridine instraspinally...	Recovered	
14	♂	3	Positive	Sulfapyridine; serum and sodium sulfapyridine intraspinally	Died	Block
15	♀	1¼	Positive	Fothergill's serum plus complement; sodium sulfapyridine intraspinally; sulfapyridine	Died	
16	♂	3	Positive	Sulfanilamide; sulfapyridine; sodium sulfapyridine and serum intraspinally	Recovered	
17	♂	1⅛	Negative	Sulfapyridine; sodium sulfapyridine and serum intraspinally	Died	
18	♂	3	Negative	Sulfanilamide; sulfapyridine; sodium sulfapyridine in vein; sodium sulfapyridine with and without serum intraspinally	Died	
19	♀	4	Negative	Sulfapyridine; sodium sulfapyridine in vein.....	Recovered	Responded within 3 days
20	♀	2	Positive	Sulfapyridine; sodium sulfapyridine intraspinally and in vein	Died	Diagnosis made 2 weeks after onset
21	♂	3	.....	Sulfapyridine orally; inadequate dose; sodium sulfapyridine intravenously	Died	Double otitis media and clinical mastoiditis; no operation
22	♀	5½	Negative	Sulfapyridine orally; sodium sufapyridine and serum intraspinally; mastoidectomy	Recovered	Relapse; otitis, mastoiditis
23	♂	1 yr. 1 mo.	Negative	Sulfapyridine orally; sodium sulfapyridine and serum intraspinally	Died	Block
24	♂	4	Negative	Sulfapyridine orally; sodium sulfapyridine intravenously	Recovered	No treatment instraspinally
25	♀	9 mos.	Negative	Sulfapyridine orally; sodium sulfapyridine intravenously and intraspinally; small amount of serum intraspinally	Died	
26	♂	22	.....	Sulfapyridine orally; sodium sulfapyridine and serum intraspinally	Recovered	
27	♀	8	Positive	Sulfapyridine orally; sodium sulfapyridine and serum intraspinally; later sulfamethylthiazole orally	Recovered	Ethmoiditis; operation
28	♂	35	Negative	Sulfapyridine orally; sodium sulfapyridine and serum intraspinally	Recovered	Followed submucous resection and ethmoidectomy
29	♀	8 mos.	Negative	Sulfapyridine orally; sodium sulfapyridine and serum intraspinally	Died	

Twenty-nine cases; fourteen recoveries.

We are reporting a series of twenty-nine cases in all of which the diagnosis was definitely established by culturing the organisms from the spinal fluid.

Table 2 shows an analysis of the data with regard to these cases. It will be noted from this table that this form of meningitis is essentially a disease of early childhood, twenty of the patients being less than 5 years of age.

Blood cultures were obtained in twenty-six instances, eight of which were positive. From this small series of cases it would seem that a positive blood culture is an adverse factor in the prognosis, since all but two of the recoveries were in the group with negative blood cultures.

While this form of meningitis appears to be a primary disease in most instances, it is nevertheless important

In this group of twenty-nine cases there were fourteen recoveries. It may be noted that among the fifteen fatal cases there were two with brain abscess, three with block and one in which the diagnosis was made and treatment started after the illness had existed two weeks.

Sulfapyridine and sodium sulfapyridine were administered in much the same manner as described in the treatment of pneumococcic meningitis. In the majority of the cases a specific serum often combined with sodium sulfapyridine was injected intraspinally. It should be noted, however, that sulfapyridine or sodium sulfapyridine or both were used without serum in five of the cases in which recovery occurred.

An endeavor to find a satisfactory method of treating meningitis due to H. influenzae is particularly impor-

tant, since for the past several years there has been a sharp increase in the incidence of this disease. This increased prevalence has been noted not only in New York but also in Boston by Fothergill.

SUMMARY

We have presented a series of thirty cases of pneumococcic meningitis with ten recoveries and twenty-nine cases of meningitis due to H. influenzae with fourteen recoveries treated with sulfapyridine, its sodium salt or both. A specific serum was usually employed as well. However, we believe, in view of our previous experience, that the lower case fatality in both forms of meningitis is attributable largely to this form of chemotherapy.

NEW CLINICAL ASPECTS OF THE ANALGESIC ACTION OF MORPHINE

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Morphine is considered the best pain relieving drug which the clinician has at his disposal, yet there are elements of tolerance, addiction and gastrointestinal disadvantages to its use. It is common knowledge that the drug often causes undesirable constipation. Further, when morphine is given over long periods of time, tolerance develops, and addiction may be the end result. Treadway [1] reports that of a series of 1,276 morphine addicts 325 attributed their original downfall to medical use of this drug. Other authors give conflicting reports, but it is interesting that Adams [2] states that in Great Britain all the witnesses called before the Departmental Committee except one considered the medical use of morphine as the immediate exciting cause of addiction in a "considerable proportion of drug habitués." Still another drawback to morphine is the frequent necessity of giving large doses, which more quickly leads to tolerance and addiction.

Much work has been done on producing a chemical which might serve as a substitute for morphine. The most notable is, perhaps, dilaudid hydrochloride (dihydromorphinone hydrochloride). It is recognized that, while dilaudid hydrochloride may have certain advantages over morphine, it does not entirely fulfil the requirements for a perfect substitute. As regards other substitutes, Hayman and Fox [3] have reported that pantopon [4] in comparable doses has no advantages over morphine.

The present report considers the use of prostigmine methylsulfate in combination with morphine in a series of approximately 100 cases.

Prostigmine is the dimethylcarbamic ester of m-oxyphenyltrimethyl ammonium methylsulfate. Pharmacologically it is similar to physostigmine salicylate in that it is a stimulant of the parasympathetics and has the power of inhibiting the cholinesterase. It does have the advantage over physostigmine of showing little, if any, miotic or untoward cardiac effects and of having greater stimulating action on the small intestine. Recently it has been shown by Schweitzer, Stedman and Wright [5] that prostigmine methylsulfate is the only therapeutic anticholinesterase drug which has a central depressant effect.

The use of prostigmine methylsulfate in myasthenia gravis is now well accepted. Recently it has been used with apparent success in the treatment of deafness.[6] Further, its use to treat and prevent postoperative ileus and anuria is well established. The rationale in myasthenia gravis and postoperative use rests on the ability of this drug to protect acetylcholine against being destroyed by cholinesterase. The premise as regards deafness is not, at the moment, perfectly clear.

Since Slaughter and Munsell [7] recently reported that prostigmine methylsulfate potentiates the action of morphine on pressure-pain in cats, it seemed plausible to try out such a combination on the human being. That prostigmine methylsulfate is a safe drug in itself has been shown by Schwerk,[8] Tietze [9] and others.

The data on patients was obtained from the Robert B. Green Memorial Hospital at San Antonio, Texas, under the supervision of Dr. Alexander Mileau, and from the Edinburgh County-City Hospital at Edinburgh, Texas, under the direction of Dr. L. M. Southwick.

A critical evaluation was made of the following factors:

1. Study of effects of prostigmine methylsulfate-morphine as to effectiveness on different types of pain.
2. Untoward effects of such a combination of drugs.
3. The use of varying dosage of morphine with prostigmine methylsulfate.
4. Determination as to whether or not the combination of these drugs leads to addiction and whether there are withdrawal symptoms after long usage.
5. The use of prostigmine methylsulfate in treating addiction.

RESULTS OF TREATMENT

The patients in this study roughly fall into six groups: (1) trauma, (2) preoperative sedation, (3) postoperative treatment, (4) coronary occlusion, (5) miscellaneous cases and (6) addiction.

1. *Trauma.*—There were approximately fifty cases in this series. They consisted of trauma due to gunshot wounds, stabbings, fractures (simple and compound) and other types of extensive trauma in which the pain made morphine mandatory. As a rule only 8 mg. of morphine with 1 cc. of a 1:2,000 solution [10] of prostigmine methylsulfate was given subcutaneously. In these patients apparent relief of pain came on in from two to ten minutes. In other accident cases of a similar nature in which only 16 mg. of morphine was administered as much relief from pain was not obtained and the onset of relief was longer, i. e. from six to twenty minutes. These observations were made from the time of the injection to the time the patient expressed real relief from pain and discomfort.

Only one minor, aged 15, received this treatment. He experienced excellent relief and there were no untoward effects.

The prostigmine methylsulfate used in this study was furnished by Hoffmann-La Roche, Inc., Nutley, N. J.

1. Treadway, W. L.: Further Observations on the Epidemiology of Narcotic Drug Addiction, Pub. Health Rep. **45**: 541 (March 14) 1930.
2. Adams, E. W.: Drug Addiction, New York and London, Oxford University Press, 1937, p. 58.
3. Hayman, J. M., and Fox, Herbert: Comparison of the Analgesic Action of Pantopon and Morphine Sulfate, J. A. M. A. **109**: 1813 (Nov. 27) 1937.
4. Pantopon is no longer included in New and Nonofficial Remedies.
5. Schweitzer, Alfred; Stedman, E., and Wright, S.: Central Action of Anticholinesterases, J. Physiol. **96**: 302 (Aug.) 1939.
6. Davis, Carroll T., and Rommel, John C.: Treatment of Deafness and Contiguous Nervous Disorders with Prostigmine, Arch. Otolaryng. **29**: 751 (May) 1939.
7. Slaughter, Donald, and Munsell, Donald W.: Some New Aspects of Morphine Action: Effects on Pain, J. Pharmacol. & Exper. Therap. **68**: 104 (Jan.) 1940.
8. Schwerk, G.: Our Experience with Prostigmine, Deutsche med. Wchnschr. **58**: 412 (March) 1932.
9. Tietze, H.: Regarding the Intravenous Use of Prostigmine, Deutsche med. Wchnschr. **60**: 402 (March) 1934.
10. Dose of prostigmine methysulfate used in each case.

2. *Preoperative Sedation.*—There were twenty-five cases in this group. Most of them were gynecologic but five appendectomies were included.

By trial, the administration of 5 mg. of morphine plus prostigmine methylsulfate four hours before surgical operation and repeated one hour before the operation proved unsatisfactory in producing sufficient sedation.

Further trials established the following routine as giving the most adequate preoperative sedation:

1. Phenobarbital 0.2 Gm. the night before operation.
2. Phenobarbital 0.2 Gm. four hours before operation.
3. Morphine 8 mg. plus prostigmine methylsulfate thirty minutes before operation.

This schedule appeared to give as good sedation as substituting 16 mg. of morphine instead of the 8 mg. plus prostigmine methylsulfate. At the time of operation this use of prostigmine methylsulfate did not interfere with any surgical procedure. All appendixes were removed in the gynecologic cases, if present.

3. *Postoperative Relief from Pain.*—All these patients had orders for 8 mg. of morphine plus prostigmine methylsulfate on return from the operating room, to be repeated every three hours for three doses and then "as needed." There were five cases of moderate distention in this series following operation. These were relieved by the insertion of a rectal tube and the administration of 0.5 cc. of a 1:2,000 solution of prostigmine methylsulfate every twenty minutes for two doses and then every two hours for four doses if needed. Only one patient required the use of a Wangensteen suction.

4. *Coronary Occlusion.*—Five patients with conditions diagnosed as coronary occlusion were treated in the emergency room with 8 mg. of morphine plus prostigmine methylsulfate. All received relief within ten minutes. They then were given this combination every three hours "as needed." In none of these cases was it necessary to order additional doses of morphine. Three received this form of treatment until death, i. e. from eight to thirty-six hours. The other two were discharged after a few days of hospitalization on this treatment. Previously such patients had always received 16 mg. of morphine. We felt that the results of the combination were as good as followed the use of larger doses of morphine.

5. *Miscellaneous Cases.*—These included bronchiectasis, delirium tremens, kidney abscesses, nephritic pains and the dressing of painful wounds. They required morphine. A typical case follows: A patient with nephritis suffered extreme lumbar pain which 16 mg. of morphine did not alleviate. The combination of 8 mg. of morphine plus prostigmine methylsulfate gave and maintained comfort.

6. *Addiction.*—Only one case of true addiction is presented. The patient was treated over a period of six weeks. He had urethral calculi with periurethral abscesses.

Six years previously he had gonorrhea, followed in one year by stricture of the urethra. At this time he entered the hospital for a urethrotomy. Soon after this operation, periurethral abscesses and a urethral fistula developed which persisted until the present time. At intervals, urethral calculi complicated the picture. The patient was an ambulance driver who gave no history of any drug habits before the urethrotomy. After operation he was given 10 mg. of morphine for pain relief. It became necessary to increase this dose to 16 mg. of this drug. Shortly the patient became addicted and took as much as 30 mg. at intervals. Three years of this habit brought his admittance to a government hospital. After the hospital discharged him as cured of the drug habit, his urethral difficulties returned and a physician put him back on morphine for relief of pain. He continued to take 16 mg. of morphine. Six weeks prior to admission to the Robert B. Green Memorial Hospital, with the diagnosis of periurethral abscesses, urethral calculi and urethral fistula, he stated that he was taking 30 mg. of morphine every four hours.

A radical urethroplasty was successfully performed. Postoperatively he was placed on 30 mg. of morphine. Two days later 16 mg. of morphine plus prostigmine methylsulfate apparently satisfied him. Reduction of the dose of morphine to 10 mg. gave excellent results for four days. Further reduction to 8 mg. did not suffice.

During this stage of the treatment he had not been told of the use of prostigmine methylsulfate but did comment that his bowel action had returned to normal. When he was told of this treatment, he cooperated well. The wound had healed after four weeks and the catheter had been withdrawn. Voluntary urination was instituted after two trials. At this time 10 mg. of morphine plus prostigmine methylsulfate was still being given and the patient did very well, complaining only of slight nervousness just before his dose. This procedure continued through the fifth postoperative week.

The sixth week 8 mg. of morphine plus prostigmine methylsulfate was ordered. After the second day of this treatment the patient skipped every other dose without ill effects. He was then discharged to a government hospital for observation.

During the time prostigmine methylsulfate was used with the morphine, no withdrawal symptoms were noted.

COMMENT

This study indicates that one-half the accepted dose of morphine when combined with prostigmine methylsulfate in doses of 0.5 mg. gives as good relief as the larger dose of morpine. There were no side reactions noted. An order for 0.5 mg. of atropine was always written, but it was never needed. No apparent tolerance to morphine when used in this combination becomes evident.

There was one case of ruptured appendicitis complicated by peritonitis in which this combination gave satisfactory results. Saegesser [11] has reported the use of prostigmine methylsulfate in a series of approximately thirty cases of peritonitis. He comments on the excellent results and says that the untoward effects in this condition make this drug suitable for use as a prophylactic to lessen the danger of postoperative intestinal atony. In our series of cases there were none which showed ileus or anuria following operation.

In all but two cases the combination of prostigmine methylsulfate and 8 mg. of morphine relieved pain. Twice in this series of 100 cases it was necessary to give 16 mg. of morphine instead of the smaller dose; one was a case of extensive gunshot wounds and one of compound fracture.

While no untoward effects were observed following the use of this combination, it is felt that perhaps shock is a contraindication to the use of prostigmine methylsulfate with morphine.

We feel that combinations of 1 cc. of a 1:2,000 solution of prostigmine methylsulfate plus 8 mg. of

11. Saegesser, M.: Prostigmine "Roche," Schweiz. med. Wchnschr. **63**: 366 (April) 1933.

morphine is an efficient pain reliever. Further, it is an excellent preoperative sedative and postoperative analgesic. When used before operation, it definitely minimizes ileus, distention and anuria. Levis and Axelman [12] believe that without prostigmine methylsulfate from 60 to 75 per cent of patients will suffer from one or the other of these conditions. Used postoperatively, enemas and the use of catheterization are decreased.

The one case of addiction treated with prostigmine methylsulfate lends encouragement to the use of this drug in similar cases.

The results in this study would seem to substantiate the experimental work done on this problem. We believe that they bear out the findings of Slaughter and Munsell [7] that morphine is a cholinergic drug as regards its action on pain. That it is cholinergic in other respects is evidenced by the reports of Slaughter and Gross [13] on the dog's intestine, cat's blood pressure and toxicity in rats.

Summary Comparing Analgesic Effects of Morphine Alone and in Combination with Prostigmine Methylsulfate and Phenobarbital

Drug Used	Dose	Time for Onset of Action	Mode of Onset	Duration of Action
1.* Morphine sulfate	16 mg.	6-20 min.	Gradual	60-90 minutes
2.* Morphine sulfate Prostigmine methylsulfate	8 mg. 0.5 mg.	2-10 min.	Increased over 16 mg. of morphine alone	90-120 minutes †
3.‡ Morphine sulfate Prostigmine methylsulfate	5 mg. 0.5 mg.	6-20 min.	Gradual	30-60 minutes
4.‡ Phenobarbital 4 hrs. before surgery Phenobarbital 1 hr. before surgery Morphine sulfate plus Prostigmine methylsulfate, 30 min. before surgery	0.2 Gm. 0.2 Gm. 8 mg. 0.5 mg.	5-10 min.	Gradual	Satisfactory sedation preceding and during anesthesia; most patients in this report received spinal anesthesia when surgery was performed

* Used for relief of pain.
† In several instances, the duration of action exceeded 120 minutes.
‡ Used for preoperative sedation.

One of us is at present investigating the angle of tolerance and addiction in dogs, and preliminary work indicates that prostigmine methylsulfate lessens the tolerance and decreases the chances of addiction to morphine.

It is hoped that this report will stimulate other clinical research as regards this problem.

SUMMARY

1. Excellent relief from pain in a variety of cases was obtained by using 1 cc. of a 1:2,000 solution of prostigmine methylsulfate with decreased amounts of morphine.

2. There were no untoward effects in this group of patients using such a combination.

3. Prostigmine methylsulfate relieves the tonic constipation caused by morphine, since it has a marked stimulatory effect on intestinal peristalsis.

4. Further large scale use of this combination in the relief of pain and in the treatment of addiction is indicated.

5. This work further substantiates the cholinergic action of morphine with regard to its effects on pain.

12. Levis, W. R., and Axelman, E. L.: Modern Method for Prevention of Postoperative Distention, Am. J. Surg. **32**: 308 (May) 1936.
13. Slaughter, Donald, and Gross, E. G.: Some New Aspects of Morphine Action, Effect on Intestine and Blood Pressure; Toxicity Studies, J. Pharmacol. & Exper. Therap. **68**: 96 (Jan.) 1940.

INFLUENZAL MENINGITIS

REPORT OF TWO CASES WITH RECOVERY; ONE CASE COMPLICATED BY PAROXYSMAL TACHYCARDIA

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DREXEL HILL, PA.
AND
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LANSDOWNE, PA.

In 1933 two cases of influenzal meningitis were presented by one of us (E. L. N.) before the Philadelphia Pediatric Society.[1] One resulted in complete cure; the other showed at autopsy a brain almost entirely devoid of exudate. We believed that death occurred in the second case either because of edema of the brain from serum shock or from pressure changes following cisternal drainage. Both these patients were treated with serum, the first with serum of Dr. Dorothy Wilkes Weiss,[2] obtained from Parke Davis & Co., the second largely with serum obtained from Dr. Margaret Pittman [3] of the Rockefeller Institute.

Two further cases of influenzal meningitis are here presented. We believe that they will be of interest because they were consecutive cases with prompt recovery; further, they presented features of interest, particularly the boy aged 5 years, who had an attack of paroxysmal tachycardia.

REPORT OF CASES

CASE 1.—V. S., a white girl aged 5 years, the daughter of a physician, on the evening of Dec. 29, 1939, felt ill, vomited twice and complained of weird and fantastic dreams. She had a rhinitis. The following afternoon she had projectile vomiting and became semicomatose. Twitchings of the upper extremities were observed; she had a high temperature. Neither her past history or her family history was relevant.

She was admitted to the Mercy Fitzgerald Hospital. She was quite stuporous but moved restlessly in the bed. Muscle twitchings were present in all extremities.

Her eyes were deviated, the pupils equal but dilated and reacting sluggishly to light. The fundi were normal. There was no evidence of intracranial pressure at this time.

The pharynx was definitely injected and hyperemic. The sinuses and mastoids were clear and remained so.

Moderate rigidity of the neck was present. Knee jerks could not be obtained. Kernig's sign was positive and Babinski's sign and ankle clonus were not present.

Her pulse rate was 168 a minute, of poor volume but regular. Her respiratory rate was 44, her temperature 105 F.

The blood count on admission was hemoglobin 9.8 Gm., red blood cells 3,510,000, leukocytes 4,550, neutrophils 80 per cent, lymphocytes 12 per cent and monocytes 8 per cent. A complete list of blood counts is given in table 2.

Blood cultures taken at this time and again on Jan. 13, 1940, were negative.

The first spinal fluid withdrawn was opalescent and contained 3,200 cells per cubic centimeter. Pleomorphic influenza bacilli were present and the culture was positive for Bacillus influenzae.

She was immediately given a transfusion of 175 cc. of citrated whole blood followed by intravenous injection of 45 cc. of 5 per cent solution of sodium sulfapyridine. A few minutes later she had a severe convulsion, became cyanotic and had extreme respiratory difficulty. The convulsion stopped after a short time and respiration and color improved.

Owing to lack of space, this article appears here without the tables. They will be included in the authors' reprints.

1. Noone, Ernest: Influenzal Meningitis and Its Treatment with Serum (Abstr.), Am. J. Dis. Child. **46**: 221-222 (July) 1933.
2. Weiss, Dorothy Wilkes, and Huntington, R. W., Jr.: J. Pediat. **9**: 462-466 (Oct.) 1936.
3. Pittman, Margaret J.: Exper. Med. **58**: 683-706 (Dec.) 1933.

Sulfapyridine was continued by mouth, averaging 4 Gm. a day. (The patient's weight was 38 pounds [17 Kg.]).

The following day she remained comatose; rigidity of the neck was extreme. The left ear drum became red and paracentesis was performed by Dr. Cornelius McCarthy. Smear and culture of the exudate were negative.

Influenzal serum had been obtained from the Mulford Laboratory of Sharp & Dohme and 50 cc. was given by vein with another blood transfusion of 100 cc.

On the following day, January 11, Fothergill's influenzal serum was received from the Massachusetts Department of Health and 8 cc. was administered into the spinal canal. This was accompanied by 5 cc. of human complement, thus following the procedure advised by Ward and Fothergill.[4] Lack of complement in diseases due to gram-negative organisms was pointed out in 1924 by Kolmer[5] and again in 1932 by Ward and Wright.[6]

The amount of serum and complement administered by spinal route was limited by the amount of thickened spinal fluid we were able to withdraw.

Thereafter, the Sharp & Dohme serum was administered intravenously and the Fothergill serum as well as some Sharp & Dohme serum by way of the spinal canal.

A survey of treatment and the condition of the spinal fluid is given in table 1. Progress of the case is depicted in figure 1.

Nausea and vomiting occasionally interrupted the oral administration of sulfapyridine, on which occasions rectal administration of the sodium salt was employed.

On the third hospital day, Jan. 1, 1940, spinal fluid cultures were negative but bacilli were still observed in the smear, an experience contrary to our observations in cases prior to the use of sulfapyridine.

The child was still stuporous on January 2 but reacted more hopefully the next day.

January 5, no fluid could be obtained on spinal tap. No pressure was registered on the manometer, and the Queckenstedt test was positive. We do not like to resort to cisternal drainage in these cases unless it is imperative. Later in the day a satisfactory flow of fluid was obtained.

January 6, serum reaction appeared, consisting chiefly of wheals and an elevated temperature, and was a continued feature of the case for several weeks.

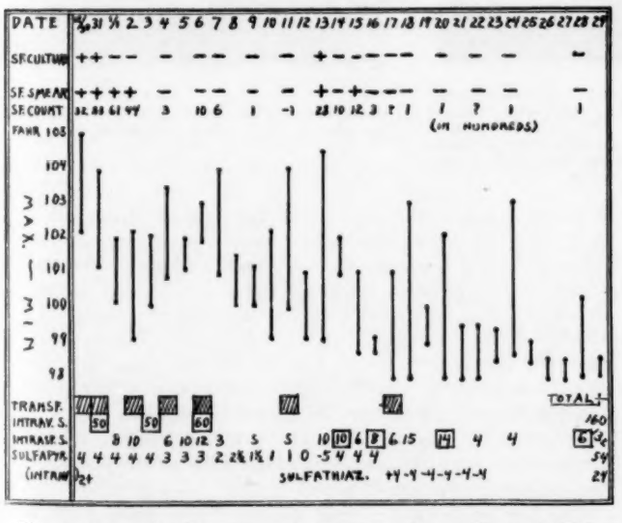

Fig. 1 (case 1).—Progress and treatment chart. Sharp & Dohme serum designated in blocks. Other serum employed is Fothergill's. *S. F.*, spinal fluid.

The mucous membrane of the lips and mouth and particularly of the gums were now covered with a dirty gray exudate. The gums were spongy. A similar finding was described by Moore and Forbes,[7] in a case of pneumococcic meningitis and was attributed by them to the sulfapyridine employed.

Dosage of sulfapyridine was decreased and no serum was given for five days.

Bacilli reappeared in smear and on culture January 13. Sulfapyridine administration was increased and serum was again given. Again culture was negative prior to the disappearance of bacilli from the smear. After January 15 both cultures and smears remained negative. With the exception of moderate serum reactions, the child steadily progressed to a completely normal state.

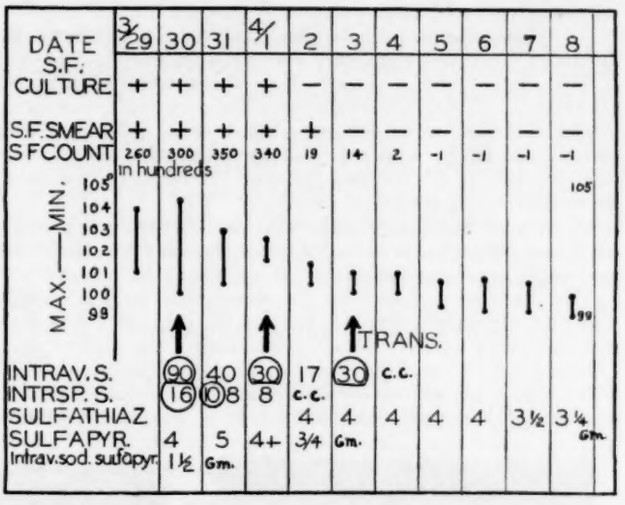

Fig. 2 (case 2).—Progress and treatment chart. Sharp & Dohme serum encircled. Other serum employed is Fothergill's. *S. F.*, spinal fluid.

January 17 sulfathiazole (Squibb) was obtained through Dr. Harrison Flippin and Dr. John Scott, and sulfapyridine was discontinued. Freedom from nausea followed the administration of sulfathiazole.

Later, neurologic examination by Dr. George Wilson showed that the child was completely normal.

CASE 2.—S. H., a white boy aged 5 years, weighing 45 pounds (20 Kg.), recovered more promptly than the first patient and presented the interesting complication of paroxysmal tachycardia.

In earlier years the boy manifested a tendency to hypersensitivity of the mucous membranes and overgrowth of the nasopharyngeal lymphoid tissue. His tonsils and adenoids were removed at the age of 2 years. However, throughout the year of the present infection he had been in excellent health and general physical condition.

March 26, 1940, while sitting on the edge of the bathtub, he fell backward and struck his head heavily in the occipital region on the opposite side of the tub. One may speculate on the influence this accident may have had in opening up pathways of infection and promoting the attack of influenzal meningitis. Certainly there are many cases of meningitis on record immediately preceded by skull fracture.[8] In this case there was no demonstrable fracture.

The following day he complained of headache. March 28 he returned from school at noon feeling ill, became nauseated and vomited all afternoon. That evening he was irritable and his reflexes were irregular. Kernig's sign was thought to be positive and his pupils were dilated. There was a heavy odor of acetone on his breath.

On the following morning he was admitted to Mercy Fitzgerald Hospital with a provisional diagnosis of head injury. He was intermittently irrational and very restless, his face was flushed and his eyes were rolling. His pupils reacted slowly to light and in accommodation, the left being larger than the right. There was medial strabismus and photophobia. His

4. Ward, H. K., and Fothergill, L. D.: Influenzal Meningitis Treated with Specific Antiserum and Complement, Am. J. Dis. Child. **43**: 873 (April) 1932.
5. Kolmer, J. A.: Proc. A. Research Nerv. & Ment. Dis. **4**: 71, 1924.
6. Ward, H. K., and Wright, Joyce: J. Exper. Med. **55**: 223 (Feb.) 1932.
7. Moore, Mary L., and Forbes, Roy P.: J. Pediat. **16**: 347 (March) 1940.
8. Prinz, H.: Chirurg **5**: 544-547 (July 15) 1933.

lips were cherry red. There was no discernible inflammation of the upper respiratory tract or of the ears.

Cervical rigidity was present but intermittent in intensity. He had a bilateral positive Kernig sign. His abdominal reflexes were present, the Babinski sign was not present and the plantar reflex and knee jerks were obtainable.

The temperature was 103 F., the pulse rate 140 and the respiratory rate 32.

X-ray examinations of the skull and cervical vertebrae for fracture or pressure signs were entirely negative.

The white blood cell count was 28,150 cells, 83 per cent neutrophils, 12 per cent lymphocytes and 5 per cent monocytes. Blood chlorides were 476 mg., blood sugar 128 mg., urea nitrogen 10 mg. per hundred cubic centimeters and blood carbon dioxide capacity 32 volumes per cent. A blood culture taken at this time was negative.

On lumbar tap cloudy fluid was obtained under a pressure of 40 mm. of mercury. The cell count was 26,000, polymorphonuclear cells predominating.

The organism observed in the smear was at first thought to be the meningococcus. Accordingly the boy was given 15 cc. of antimeningococcus serum intraspinally and later, when obtained, 20,000 units of Ferry's meningococcus antitoxin in 120 cc. of 5 per cent dextrose solution intravenously. Further amounts of 5 per cent dextrose as well as Hartmann's solution were given into the vein to effect mineral balance. Sulfanilamide 1.5 Gm. was given by mouth on this date, the 29th.

On the following morning, the 30th, the diagnosis of Pfeiffer's bacillus was determined and treatment started with anti-influenzal serum and sulfapyridine. The dosage is summarized in figure 2 and table 3. An initial dose of sodium sulfapyridine was given, 1.5 Gm. in 5 per cent solution, which was followed by a mild reaction consisting of a brief period of respiratory irregularity and muscular tremors.

At this time the child was acutely ill and delirious, his neck was very rigid and his general posture was that of opisthotonos; his knee jerks were no longer obtainable. He picked continuously at the bed clothes and maintained a disconnected discourse in a drawling voice. He exhibited photophobia, and his left pupil was still larger than the right. The spinal fluid was thick and under high pressure, yet on the evening of that day there was a partial block. Manometer pressure was from 0 to 3 mm. of mercury and only 3 cc. could be withdrawn. By morning there was a free flow of fluid.

Since the child had severe reactions when intraspinal serum was used in this case, the serum was given chiefly by vein. The amounts are presented in figure 2 and table 3.

April 1 urticaria was noted, and this continued for ten days after the last administration of serum. The heart appeared to be somewhat enlarged but the beat was regular and the sounds were of good quality. There was no enlargement of the liver. Cyanosis was present, apparently from the sulfapyridine.

During the night of April 2 an attack of paroxysmal tachycardia began. The rate as registered by the electrocardiograph was 230 a minute. The beats were of good quality early in the day and of poorer quality in the afternoon. The heart was enlarged. The enlargement was confirmed by examination with a portable x-ray apparatus conducted by Dr. J. S. Lehman. There was no suggestion of pericardial effusion. Increased bronchovascular markings in the inner third of the lung fields were compatible with the effect of minimal pressure of active pulmonary hyperemia.

The boy lay quietly in bed as though afraid to move. The vessels of the neck pulsated. There was not much cervical rigidity. The abdomen was flat and there was no enlargement of the liver.

Electrocardiographic studies performed by Dr. Edward Torrance are shown in figures 3, 4 and 5. Tracings were made during the attack, immediately after the attack and eighteen days later. In the opinion of Dr. Torrance, the tracing taken after the attack shows left axis deviation due to dilatation.

Pressure was made over the carotids without effect, but in our opinion the pressure was inefficiently performed and the failure of result inconclusive. The child was given two doses of quinidine, each 1½ grains (0.1 Gm.). The second dose was given at 4 p. m. The paroxysmal tachycardia stopped abruptly at 5:20. The pulse immediately became stronger and the rate dropped to 125 a minute and continued to lower. Fluoroscopic study by Dr. Lehman showed a definite reduction in the size of the heart as compared with the previous film study.

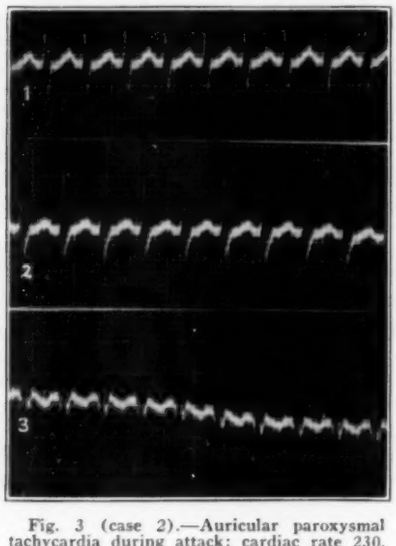

Fig. 3 (case 2).—Auricular paroxysmal tachycardia during attack; cardiac rate 230. It was impossible to distinguish P waves because of rapidity of rate. There was no evidence of cardiac damage.

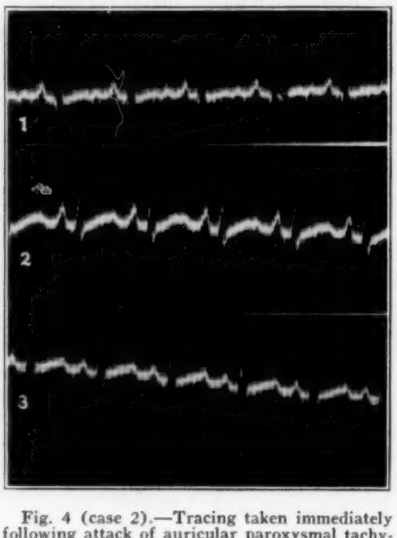

Fig. 4 (case 2).—Tracing taken immediately following attack of auricular paroxysmal tachycardia; cardiac rate 125. Note sharply peaked P waves and left axis deviation, latter probably due to cardiac dilatation during paroxysm.

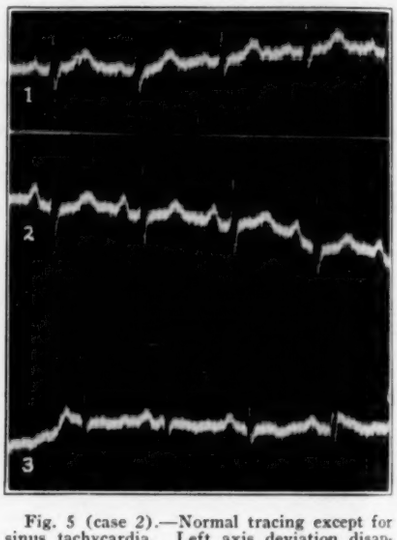

Fig. 5 (case 2).—Normal tracing except for sinus tachycardia. Left axis deviation disappeared. T waves show improvement.

The boy was rational that day. Pupillary changes were not recorded during the attack, but on the following day the left pupil was smaller than the right, the reverse of the pupillary changes during the earlier and probably initiative stages of the infection. The pupillary changes, drawling speech and tachycardia may have been influenced by inflammatory changes in the vicinity of the fourth ventricle.

The boy now made a rapid recovery. On April 3 the blood sulfapyridine level was 6 mg. per hundred cubic centimeters. From this point treatment was continued with sulfathiazole, secured through Dr. Harrison Flippin. On April 5 the liver was palpable but was no longer palpable by April 7. On the 6th he had a mild cough and his right ear contained a small amount of exudate. Paracentesis was performed by Dr. McCarthy and, as in the first case, culture was sterile. This may have been part of the serum reaction. On the 6th his knee jerks returned. His further progress was steady and uneventful.

The majority of the intraspinal and intravenous treatments were performed by Dr. P. J. Devers.

The immune serum employed was *a* supplied by the Massachusetts Department of Health and *b* supplied by the Mulford Laboratories of Sharpe & Dohme. The latter serum is prepared from six strains of Haemophilus influenzae of the Pittman type b (smooth),[9] secured from patients with mixed virulent respiratory and meningeal infections.

COMMENT

As six patients with influenzal meningitis[10] were successfully treated in the Philadelphia district during the winter of 1939-1940, there arises the possibility of the prevalence of a strain less virulent than usual. This does not appear to us to be the case. Certainly these two patients appeared as severely ill in the initial stages as other patients observed in previous years. The good results, in our opinion, can be attributed to the more recent available therapy, particularly sulfapyridine and sulfathiazole.

It is essential to make an early diagnosis. This is sometimes difficult, as is illustrated by case 2, owing to involved onset and the early pleomorphic appearance of the organism. Attention was first drawn to the pleomorphic character of influenza bacilli by Slawyk in 1899 and by many other later writers. Once the diagnosis is made, treatment should be vigorously instituted and continued until all danger of reappearance of the organism in the spinal fluid is past. Herein lies one of the chief advantages of chemotherapy, for sulfapyridine and particularly sulfathiazole can be maintained after reactions have made serum treatment embarrassing and even dangerous. However, we believe that we secured beneficial results in the use of serum alone in earlier cases and that the combined treatment with serum and chemotherapy is to the advantage of the patient.

In connection with the early institution of vigorous therapy may be mentioned the tendency of this infection, untreated, to produce heavy exudate with astonishing pressure about the base of the brain, thus accounting for its further tendency for reappearance of bacilli after apparent initial success.

SUMMARY

1. In two consecutive cases of influenzal meningitis 5 year old children were treated with serum (Fothergill and Mulford) and chemotherapy (sulfapyridine and sulfathiazole); recovery occurred in both.

2. Both cases presented interesting features. In the first case a severe shock and convulsion followed intravenous administration of sodium sulfapyridine. A grayish membrane of the lips, gums and mucous membranes of the mouth also developed, presumably due to the sulfapyridine employed. In the second case the infection was immediately preceded by an injury to the head. This case was complicated by an attack of paroxysmal tachycardia.

In both cases an exudate of the middle ear developed during the infection, the culture being sterile in both instances. Blood cultures in both cases were negative.

3. Both sulfapyridine and sulfathiazole are effective in the treatment of influenzal meningitis. There is less tendency to nausea with sulfathiazole.

Wilde Avenue and Cedar Lane.

9. Pittman, Margaret: J. Exper. Med. **53**: 471-492 (April) 1931.

10. Personal communication: Arnat, John, M.D., Episcopal Hospital, one case; Chapple, Charles, M.D., Chestnut Hill Hospital, one case; Harvie, Frederick, M.D., Service of Dr. Joseph Stokes, University Hospital, one case; Wilder, Theodore, M.D., Abington Hospital, one case. Dr. Harvie's case is particularly interesting because the child was only 21 months old. Dr. Chapple's patient was 2½ years of age. Both these children were treated with sulfathiazole.

SPONTANEOUS REDUCTION OF CERVICAL SPINE DISLOCATIONS

J. T. NICHOLSON, M.D.
PHILADELPHIA

Spontaneous reduction of a dislocation of the cervical spine is the restitution of normal relationship between articular facets by permitting active rotations of the head while it functions as the distraction force.

ANATOMY

The alined position of the cervical vertebrae is controlled by the opposing articular facets. If there is an abnormal distortion or loss of apposition between the articular facets a dislocation of the cervical vertebra prevails. The articular facets of the cervical spine are sliding joints. These are bound by an articular capsule and are supported by the ligaments of the cervical spine.

In the first cervical vertebra the facets are lateral masses which are joined anteriorly by a narrow arc of bone, the arcus anterior, and posteriorly by a similar but longer arc, the arcus posterior.[1] The lateral masses superiorly rest against the occipital condyles of the skull. Below they articulate with the two superior articular facets of the second cervical vertebra. The odontoid has a flattened cartilaginous surface both anteriorly and posteriorly. Across its posterior surface is stretched the transverse ligament from either lateral mass of the first cervical vertebra. From its tip run two alar ligaments and an apical ligament joining the basilar process of the skull. These ligaments are covered with the tectoria membrane, which extends from the basilar process of the occipital bone over the posterior surfaces of the vertebral bodies. The tectoria membrane in turn is covered by the posterior longitudinal ligament, which is also attached to the basilar process of the skull and the posterior surface of the vertebral bodies. Anteriorly the first cervical vertebra is supported by the anterior longitudinal ligament, which extends from the inferior surface of the basilar process of the occiput attaching along the anterior surface of the vertebral bodies. Joining the arcus posterior to the posterior margin of the foramen magnum is the atlanto-occipital membrane. The lower margin of the arcus posterior is joined to the second cervical lamina, and this lamina in turn to the third and it and the successive laminas by ligamenta flava. The inferior facets of the second vertebra are relatively further posterior than the superior and are transitional toward a lateral plane with the articular surface obliquely anterior and caudad. In turn the corresponding superior facets of the third cervical vertebra have a position with the articular surface obliquely posterior and cephalad. Successive articulations of the lower vertebrae in the cervical region are more in the lateral plane but otherwise are similar to those between the second and the third. Interposed between the vertebral bodies excepting the first and second is a fibrocartilage disk. This is covered anteriorly by the continuation of the anterior longitudinal ligaments and posteriorly by the posterior longitudinal ligament.

From the Orthopaedic Clinic of the Children's Hospital.
Read before the Section on Orthopedic Surgery at the Ninety-First Annual Session of the American Medical Association, New York, June 12, 1940.

1. Spalteholz, Werner: Hand Atlas of Human Anatomy: VI, Philadelpha, J. B. Lippincott Company.

CLASSIFICATION

The dislocation is common in the upper two cervicals. This may be due to the leverage of the head and the horizontal position of the facets. The dislocation is described as anterior, right or left rotary, posterior

Fig. 1 (case 2).—Side view of the typical position of the head with a right unilateral rotary dislocation of the first cervical vertebra.

and right and left lateral. A fracture of the odontoid or the accessory processes generally accompanies the latter two types. Both articular facets are displaced in all but the rotatory dislocations.

ETIOLOGY

Cervical dislocations may result from trauma, infection, paralysis or congenital defect. Traumatic dislocations are frequently associated with a fractured odontoid or an accessory process. Automobile accidents, falls on stairs, falls from bed, sudden turns of the head, and postoperative overcorrection of torticollis are some of the associated accidents.

Following infection, either in the vertebral bodies or in adjacent cervical tissues, the dislocation is occasionally spontaneous.[2] The ligaments supporting the cervical vertebrae become relaxed as a result of bone destruction, joint distention or bone decalcification. The vertebrae are destroyed by pyogenic, tuberculous or syphilitic osteomyelitis. The distention of the joints may be from the hyperemia induced by the adjacent infection or from direct extension of infection, such as sinusitis, pharyngitis, tonsillitis, mastoiditis, adenitis and dental abscesses through the neighboring cervical tissues. Decalcification of bone has been reported in the presence of hyperemia resulting from an associated infection.[3]

Paralytic dislocations from muscle imbalance have occurred in the subacute stage of poliomyelitis.[4]

Congenital absence of the odontoid [5] and anomalies in the cervical facets are responsible for some cervical dislocations.

DIAGNOSIS

There are definite clinical manifestations which have been described by several authors that lead one to suspect a cervical dislocation. The head is held in a torticollis position. In unilateral dislocations the head is tilted to the side of the dislocation and the chin rotated away from it. The head can be flexed only a few degrees to the opposite side and the chin cannot be rotated as far to the dislocated side. The head is in flexion and extension accentuates pain. The patient frequently supports his head with his hands when rising from a prone position. The entire body is turned when the subject attempts to see over the opposite shoulder. Pain is referred to the occiput and mastoid in dislocations of the upper cervicals. These areas are sometimes tender to touch. The mouth may be difficult to open because of the flexed position of the head. If the pharynx can be seen it will be noticed to bulge to the side opposite the dislocation, if it is unilateral. The paraspinal muscles are prominent posteriorly on the side opposite the dislocation. Occasionally a sensation of grating is experienced with attempted rotation of the head. Dysphagia and voice change seldom occur.

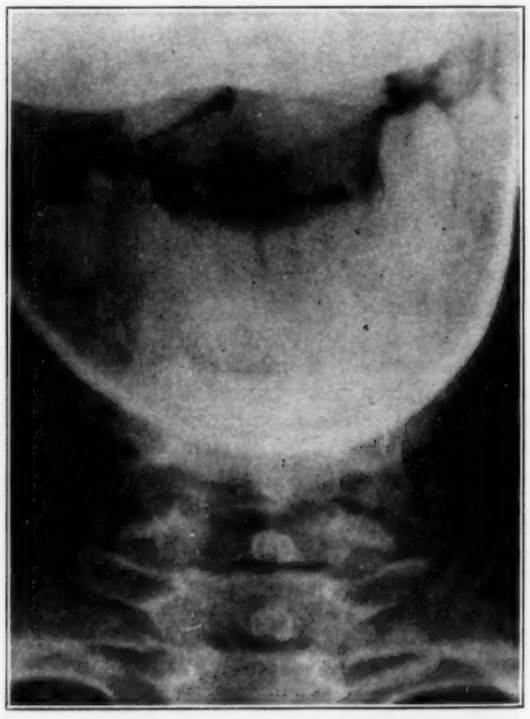

Fig. 2 (case 2).—Front view of the typical position of the head with a right unilateral rotary dislocation of the first cervical vertebra.

Paralysis is rare in the subject who survives the initial dislocation force. If there is paralysis, it is evidenced mainly in the arms.

The x-ray film verifies the diagnosis (figs. 1, 2, 3 and 4). In dislocations of the first cervical vertebra the

2. Jones, R. W.: Spontaneous Hyperemia Dislocation of Atlas, Proc. Roy. Soc. Med. **25**: 586, 1932.

3. Greig, D. M.: Fracture and Dislocations of the Odontoid, in Clinical Observations on the Surgical Pathology of Bone, Edinburgh, Oliver & Boyd, 1931. Leriche, R., and Poligard, A.: The Normal and Pathologic Physiology of Bone, St. Louis, C. V. Mosby Company, 1928.

4. Coutts, M. D.: Atlanto-Epistropheal Subluxation, Arch. Surg. **29**: 297 (Aug.) 1934.

5. Roberts, S. M.: Congenital Absence of the Odontoid Process Resulting in Dislocation of the Atlas, J. Bone & Joint Surg. **12**: 988 (Oct.) 1933.

lateral view reveals a lordosis of the cervical spine with the anterior arch of the first cervical extending anterior to the odontoid, unless the odontoid is fractured. In the other cervical dislocations the body of the dislocated vertebra projects beyond the anterior border of the vertebra. The posterior arch of the dislocated vertebra appears broader because it is tilted. The posterior borders of the vertebral bodies do not form a continuous arc but angle at the site of the dislocation.

The anteroposterior view discloses the spine of the dislocated vertebra pointing to the opposite side from which the chin is rotated. The spinous prcoesses of successive vertebrae gradually appear toward the midline.[4] Visible between the first and second vertebrae is the greater width of one articular space. In the other cervical vertebrae there is an increased distance between the transverse processes on the one side and a decreased distance on the opposite side. In a forward displacement of the first cervical both articular spaces are decreased. In forward displacement of the other vertebrae there is a diminished distance between the transverse processes, and the intervertebral space is narrowed or obliterated. In lateral displacements the odontoid appears nearer one lateral mass than the other, and in the succeeding vertebra the transverse process and vertebral body project farther to one side.

METHOD OF REDUCTION

The spontaneous method is developed from Stookey's [6] treatment of injuries of the cervical spine in which hyperextension of the neck was obtained by compressing the upper edge of an air mattress with adhesive tape. The technic varies in spontaneous reduction in that the subject is placed recumbent with his shoulders at the upper margin of three short mattresses tiered on a fracture bed (fig. 5). The head is not supported; its weight distracts the joints of the cervical spine and holds the neck in hyperextension. No apparatus, such as a Sayre collar or skeletal traction tongues, is used. The head of the bed is elevated on shock blocks to prevent the subject from sliding. Buck's extension is employed on both legs of small children in addition to elevating the head of the bed. The position at first may be uncomfortable from strain on the anterior musculature of the neck, in which case the subject is shifted toward the foot of the bed so that the neck rests over the end of the mattress, thus receiving some support. Gradually in the following twenty-four to forty-eight hours the subject is positioned toward the upper end of the bed until the neck is beyond the mattress and the head is hanging free.

After an additional twenty-four to seventy-two hours with the head hanging free, the dislocation is found to be reduced. This is determined by the ability to rotate passively and flex laterally the cervical spine an equal distance to either side.

X-ray examination is facilitated by lifting the mattress with the subject onto a stretcher. This does not disturb the position of the head. The films are taken in the anteroposterior and lateral position without moving the head by holding the casset on the side or in back of the neck.

Reduction is maintained by a plaster bandage from head to pelvis. It is necessary to have the chin and forehead included to prevent flexion of the head, which would cause redislocation. The cast is extended to the pelvis to guard the spine against flexion and to distribute its weight on the iliac crests. The method of applying the plaster cast is an adaptation of that advocated by Brookes [7] in 1933: The subject is transferred from the mattress without supporting the head to the canvas sling of an Abbott frame so that the back rests on the sling and the head hangs dependent over the end. In this position the body jacket is applied. When this dries sufficiently to withstand pressure, a table of equal height as the sling is pushed beneath the subject. The sling is released, which permits the table to support the subject's trunk. The frame and sling of canvas are removed. A 4 inch muslin bandage with a longitudinal slit in its midportion, permitting it to be slipped over the patient's head, to run beneath the chin and occiput, is arranged so that the ends may be tied behind the operator's back.[7] In this way the operator can exert traction and control the amount of extension of the neck. The extension that occurs at the occipital-axial joint is not necessary and not desirable, as it will fix the subject's head looking heavenward and make feeding and balance difficult. The head cast is then applied over the traction bandage, which can be withdrawn after the head and body parts of the plaster cast are joined. The subject is allowed to sit up the day after the application of the plaster cast. He is permitted to walk the third day and is discharged as soon as he can navigate without difficulty.

Cervical Dislocations with Spontaneous Reduction

Case	Subject	Age, Years	Etiology	Site	Complication	Result
1	D. S.	3	Spontaneous	1st anterior	3 recurrences	Reduction; surgical fixation
2	W. S.	10	Spontaneous	1st right rotary	None	Reduced
3	B. T.	8	Spontaneous	Occiput right lateral, 1st left rotary	None	Reduced
4	C. R.	6	Spontaneous	2d right rotary	None	Reduced
5	R. J.	11	Spontaneous	2d right rotary	None	Reduced
6	M. D.	3½	Trauma	1st anterior	Fracture odontoid	Reduced
7	D. P.	5	Trauma	2d rotary	Ear infection	Unreduced
8	J. B.	7½	Trauma	2d rotary	None	Reduced
9	M. P.	4	Trauma	2d rotary	Respiratory infection	Unreduced; surgical fixation
10	J. D.	60	Trauma	1st anterior	Fracture odontoid	Reduction; delirium tremens and pneumonia; death
11	J. W.	25	Trauma	5th rotary	Fracture of 6th cervical; weakness of arm musculature	Reduction of dislocation; fracture unreduced

The dislocations are held from twelve to sixteen weeks in plaster and eight additional weeks in a Thomas collar. The Thomas collar is necessary to permit rehabilitation of the cervical muscles. These muscles have undergone marked atrophy. In this condition they fatigue readily. Strain is then thrown on the ligamentous structures of the cervical spine. This strain

6. Stookey, Byron: Treatment of Fractures: The Management of Fracture Dislocations of the Vertebrae Associated with Spinal Cord Injuries, Am. J. Surg. **26**: 513 (Dec.) 1934.

7. Brookes, Theodore: Dislocations of the Cervical Spine, Surg., Gynec. & Obst. **57**: 772 (Oct.) 1933.

causes pain and might result in another dislocation. The motion of the cervical spine permitted by the Thomas collar allows the musculature of the neck to develop without hazard of fatigue and ligament strain.

After support for the neck has been discontinued, lateral x-ray films are taken of the cervical spine in maximum extension and maximum flexion to determine potential luxation. If this exists, it is accentuated when the cervical spine is flexed (fig. 6).

COMMENT

Nine children and two adults were treated by the method described. Summaries of the cases are given in the accompanying table. Five patients had a dislocation of the first cervical vertebra. Two of these had associated trauma and a fractured odontoid. Five patients had a dislocation of the second cervical vertebra. Three of these dislocations were attributed to trauma. One adult had a fracture of the sixth cervical vertebra with a unilateral luxation of the fifth. This was the only patient who manifested neurologic signs. Two adults had traction by means of a Sayre collar with the head in hyperextension maintained until a decubitus ulcer on the chin necessitated another method to obtain reduction. One child with a spontaneous dislocation of the first cervical vertebra had three recurrences which reduced each time by the spontaneous method. This subject had traction by a Sayre collar for four weeks without reduction prior to the first spontaneous reduction. After a second surgical fixation the reduction

Fig. 3 (case 2).—Appearance after reduction.

was maintained. Two children with a traumatic dislocation of the second cervical vertebra failed to reduce spontaneously and the method was abandoned after four days because of middle ear infection in the one and acute sinusitis in the other. These subsequently failed to reduce with manipulation. One, at open operation, could not be reduced, but the laminas of the second and third vertebrae were wired. The other remains unreduced and free from symptoms with torticollis deformity. Six months after the removal of the plaster cast the patient's family moved and could not be located.

One adult had a fractured odontoid. Delirium tremens developed after his second day in a plaster

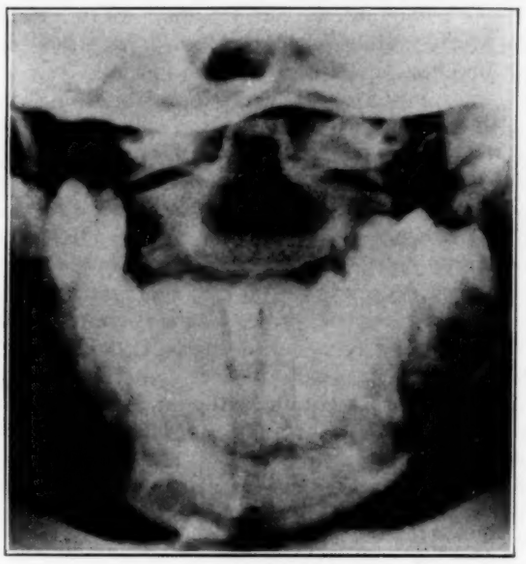

Fig. 4 (case 2).—Appearance after reduction.

cast and he tore it off. He died of pneumonia in the psychiatric ward four weeks later. The other patient had a dislocation of the fifth cervical vertebra and a coexisting compressed fracture of the sixth cervical vertebra. Extensive edema of the head developed after it had hung dependent four days. This made application of a second cast necessary, as the first became too loose to afford adequate fixation for the head after the edema subsided.

The spontaneous method of reduction is not advocated in fractures of the odontoid with posterior displacement of the first cervical vertebra or in posterior displacement of other cervical vertebrae. The hyperextended position of the head in these cases of posterior displacement could result in further posterior displacement with impingement of the cord. Taylor traction is used in posterior dislocations for alinement and a plaster cast applied in the manner described. Early in acute traumatic dislocations traction and extension by another method are advocated, especially if neurologic involvement is manifest. There is danger of increasing the edema about an injured cord with the dependent position. As the neurologic disturbance subsides the position may be gradually assumed if repeated careful examinations for sensory and motor changes are done.

REPORT OF CASES

CASE 1.—D. S., a girl aged 3 years, who was admitted to the Children's Hospital, June 2, 1936, had measles six weeks previously, followed by cervical adenitis and bilateral otitis media. The neck had been held stiffly with the head turned to the right for a week. There was anterior displacement of both lateral masses of the first cervical vertebra. Head traction by means of a Sayre collar was tried for four weeks without success. Reduction occurred in twenty-four hours when the head was allowed to hang dependent. A cast was applied from the head to the pelvis. This was changed at the end of three months and removed in four months. A Thomas collar was worn six weeks.

Jan. 4, 1937, two weeks after the removal of the Thomas collar, dislocation recurred. Reduction was accomplished with the head dependent and a cast applied on the third day. The cast was removed and a Thomas collar applied at the end of five months. A week after the removal of the Thomas collar the second time, a recurrence of the dislocation was observed. The dislocation again reduced spontaneously.

July 29, open fixation of the first and second cervical dislocation was done through a posterior midline incision. The head of the subject was held in position by means of a plaster bed. The posterior arches of the first and second cervical vertebrae were closely approximated by means of a towel clip. The arches were then lashed together by means of fascia lata from the thigh, as advocated by Osgood and Mixter. A jacket was worn for four weeks and a Thomas collar applied. The dislocation again recurred. On September 27, after spontaneous reduction, a second operation was done. The fascial suture was found to have pulled free from its silk sutures. It was then observed that a mistake had been made in not knotting the fascia to itself and securing the knot with silk. This time two wire sutures were passed around the posterior arches of the first and second cervical vertebrae and an attempt was made to obtain bony fusion between them by removing their ligaments and cartilaginous covering and overlapping pedicle grafts.

Four months later the cast was removed. The position had been maintained and a Thomas collar was applied and worn three additional months.

On June 1, 1939, twenty-one months after the second operation, the head was held with a slight tilt to the left: extension was 30 degrees, flexion 45 degrees and rotation 25 degrees left and 45 degrees right. Lateral flexion was 45 degrees and was bilateral. There were no neurologic abnormalities. X-ray examination showed no forward luxation with flexion, according to comparative lateral films with the cervical spine in maximum extension and flexion.

CASE 2.—W. S., a Negro boy aged 10 years, admitted to the Children's Hospital Nov. 16, 1936, three weeks before admission during illness from acute tonsillitis awakened one morning with pain in the mastoid region and a stiff neck, which forced him to hold his head tilted to the right and chin rotated to the left. X-ray examination revealed a forward dislocation of the right lateral mass of the first cervical vertebra. He was treated with his head hanging dependent as described. After four days x-ray examination verified reduction and a plaster jacket from the head to the pelvis was applied. March 25, 1937 (four months later), the cast was removed and a Thomas collar was applied. The latter was worn one month. On March 14, 1938, there was a questionable tilt of the head to the right. Lateral flexion of the cervical spine was 20 degrees less to the left than to the right. Other motions were unimpaired. X-ray examination proved that the reduction was maintained.

Fig. 5.—The arrangement in bed of the subject to receive dependent head traction for spontaneous reduction.

CASE 3.—B. T., a girl aged 8 years, had a prolonged history of infection of the upper respiratory tract and pharyngitis. She had had cervical adenitis for five weeks. For two weeks before admission to the Mary Drexel Home on May 9, 1938, her head had been turned with the chin on the right shoulder and head tilted anteriorly. Examination revealed the head held in 70 degrees rotation to the right and 30 degrees flexion to the left. Rotation of the head to the left failed to bring the chin within 30 degrees of the midline. Rotation of the head to the right was 100 degrees. Flexion to the right was 0. No other physical signs were present. The x-ray examination showed a rotary displacement of the atlas to the left with a luxation of the occipital condyles to the right on the lateral masses. With the head hanging dependent the dislocation reduced in forty-eight hours. The usual type of cast was applied and worn for three months. Then a leather reenforced collar was worn for two months. On April 15, 1939, x-ray examination showed that reduction had been maintained. The chin clinically was slightly to the right of the midline, but cervical motions were equal.

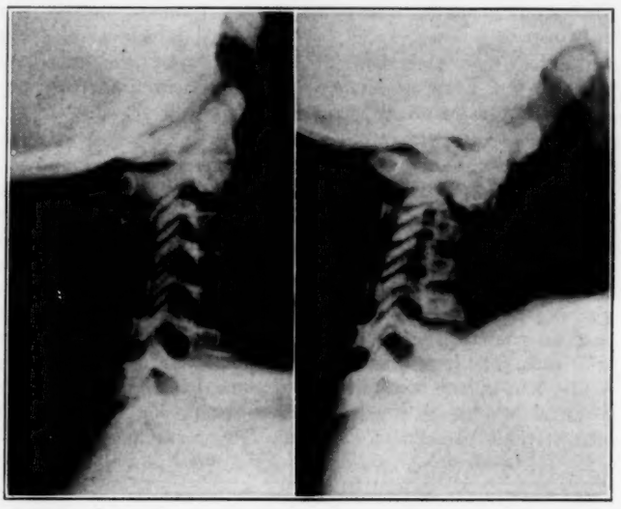

Fig. 6 (case 9).—(*a*) A unilateral right rotary dislocation of the second cervical in which reduction failed to be maintained. This can readily be demonstrated in the lateral film (*b*) with the head flexed.

CASE 4.—O. R., a Negro boy aged 6 years, had a left cervical adenitis. On admission to the Children's Hospital, the head was tilted to the right and the chin rotated to the left. X-ray examination revealed a luxation of the second right inferior facet on the third. Spontaneous reduction was accomplished in three days. Fixation was discontinued in two months. March 2, 1939, motions of the neck were symmetrical.

CASE 5.—R. J., a Negro boy aged 11 years, had an acute attack of adenitis fourteen days before admission to the Children's Hospital, Dec. 16, 1938. On this date he complained of a stiff neck and inability to straighten his head. The head was tilted to the left and the chin rotated to the right. X-ray examination revealed a second cervical dislocation. Reduction was accomplished spontaneously in twenty-four hours. The cast was worn three months, then a Thomas collar for four weeks. The last examination, April 1, 1940, revealed no restriction of motion but a slight tilt of the head.

CASE 6.—M. D., a Negro girl aged 3½ years, whose neck was stepped on by an adult forty-eight hours before admission to the Children's Hospital on Aug. 25, 1936, complained of pain in the neck and would not move her head. The head was tilted to the left and the chin was rotated to the right (fig. 7). X-ray examination showed a fracture at the base of the odontoid with anterior displacement. After forty-eight hours of dependent head traction a cast was applied from the head to the pelvis. This was worn for three months. A Thomas collar was worn for two months. May 24, 1937, there was but slight deviation of the head but full range of motion of the cervical spine. X-ray examination proved that the fracture was healed and the dislocation reduced.

CASE 7.—D. P., a boy aged 5 years, fell from bed Aug. 4, 1938. The complaint was pain on the left side of the neck and inability to move the head. X-ray examination revealed a dislocation of the second cervical vertebra. After one week the dislocation failed to reduce with dependent head traction. (Great difficulty was encountered in keeping the patient in a satisfactory position. A discharging ear also developed.) Manipulation of the neck by Taylor traction and Walton maneuver was unsuccessful. A body jacket was applied and worn for three months. Six months after the cast was removed there was no change in the position of the vertebra. The subject subsequently moved to California.

CASE 8.—J. B., a boy aged 7½ years, had a series of infections of the upper respiratory tract during the winter and had just finished convalescing from an acute pharyngitis. On March 14, 1939, he was permitted to return to school and was riding in the rear seat of a sedan when it was struck by another car. The child was thrown to the floor of the sedan and sustained a bump on the head. Examination at a local hospital was negative for injury. The child played with other children that afternoon. The following morning he awakened with a stiff neck. The head was tilted to the right and the chin rotated to the left. There was pain on attempted motion of the neck. Physical examination was negative except for pain and the characteristic position of the head. The x-ray appearance was

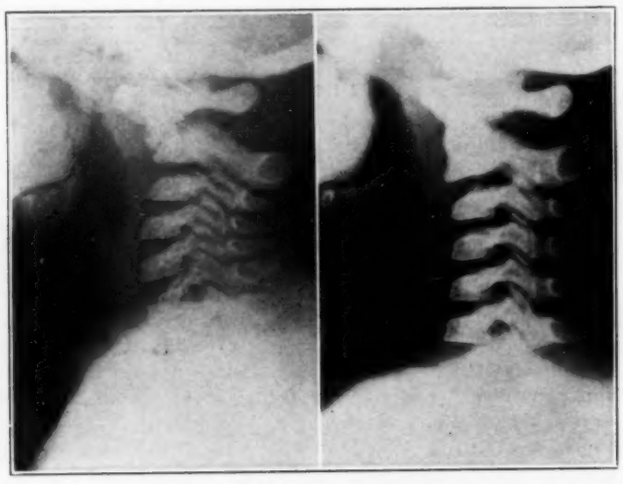

Fig. 7 (case 6).—(*a*) A fracture through the base of the odontoid with anterior dislocation of the first cervical reduced spontaneously and (*b*) united after three months of immobilization in plaster.

interpreted as a rotary displacement of the right inferior facet of the second cervical vertebra on the third. The child was hospitalized and after forty-eight hours of dependent head traction the dislocation was clinically and roentgenologically reduced. A plaster cast was applied and worn until May 12. A Thomas collar was worn for an additional month. On March 15, 1940, x-ray examination showed a normal position of the vertebrae and clinical examination was negative.

CASE 9.—M. P., aged 4 years, a feebleminded boy, fell from his crib eight days after a cleft palate operation. A dislocation of the inferior right facet of the second cervical vertebra was diagnosed by x-ray examination, Dec. 23, 1939. This dislocation failed to reduce spontaneously. An infection of the upper respiratory tract and sinusitis developed. The dislocation could not be reduced by manipulation. An open operation was done March 26, 1940, but reduction could not be obtained. Further deformity was averted by wiring the second and third cervical laminas together. June 5 the position had been maintained two weeks after plaster fixation had been removed.

CASE 10.—J. D., a man aged 60, had delirium tremens, fell down stairs May 30, 1935, sustained a fracture of the odontoid with anterior displacement of the first cervical vertebra and a fracture of the right humerus. He was admitted the same day to the Philadelphia General Hospital. There was no neurologic involvement. It was necessary to feed him through a nasal tube because of impending delirium tremens. After four days a decubitus ulcer developed on his chin from the Sayre collar traction. Dependent weight of the head was then tried. In twenty-four hours reduction had been spontaneously accomplished. A cast was applied from the head to the pelvis. He tore this cast off twenty-four hours later and was then transferred to the psychiatric ward. The dislocation recurred but no symptoms indicative of cord pressure developed up to the time of his death from pneumonia six weeks after admission.

CASE 11.—J. W., a man aged 25, on Aug. 10, 1937, dove into the breakers at the beach. He was helped from the water. His hands pained and lost their grip and he could not elevate his arms. His legs gave him no support. He was admitted to a local hospital and Sayre traction was applied. An ulcer developed on his chin after seven days.

On September 4 he was transferred to the Philadelphia Orthopaedic Hospital. He had no power in the left hand and marked weakness of the right hand, shoulders and upper arms but no sensory disturbance. The lower extremities were normal except for hyperactive reflexes.

X-ray examination revealed a forward position of the fifth cervical vertebra on the sixth with a compression fracture of the latter.

Since muscle power had steadily improved, the head was placed in a dependent position September 11. X-ray examination revealed excellent alinement five days later. There was, however, extensive edema of the scalp. A jacket was applied September 16 and the subject was ambulatory September 19. A few days later it was necessary to change the cast, as it had become loosened about the head when the edema subsided.

The reduction of the vertebral fracture was not obtained in this case, as the position of hyperextension was not maintained. The patient regained complete power in his arms, had no symptoms referable to his neck, and returned to work in four months as an electrician.

SUMMARY

A spontaneous method of reducing dislocation of the cervical spine proved applicable and successful when other methods could not be applied or had to be discontinued because of lack of the patient's cooperation, presence of infection or appearance of a decubitus ulcer on the chin. This method of reducing uncomplicated dislocation of the cervical spine was tried on nine children and two adults. The method was uniformly successful in the reduction of spontaneous dislocation. It failed in two traumatic dislocations of the second cervical vertebra. The dependent head theoretically was not applicable in all cases immediately after a traumatic injury. It should not be used in posterior dislocations. Edema of the scalp was a complication arising from the dependent position of the head of one adult. In the two failures there was a danger of spreading a respiratory infection through the sinuses or the middle ear. The reduction was determined clinically by symmetrical rotation and lateral flexion on passive motion of the head. X-ray examination was made without disturbance to the position of the head.

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ABSTRACT OF DISCUSSION

DR. W. H. VON LACKUM, New York: Dr. Nicholson has presented an interesting review of cases of the spontaneous and traumatic dislocations of lesser degree, treated by a method not previously described. In recent years much interest has been shown in lesions of the cervical spine which present this clinical picture of a painful neck, tilted to one side and rotated to the opposite side and associated with muscle spasm. They are the lesions of the atlanto-epistropheal and of the lower cervical spine, associated with trauma exudation or inflammation and an occasional case of paralysis and congenital anomaly in or about the atlanto-epistropheal and lower joints of the

cervical spine. In the atlanto-epistropheal region they are, according to Coutts, rotation deformities, distention-subluxations, dislocations and fracture dislocations. That a fine line of distinction between the rotation deformities, subluxations and slight dislocations has not been made until recently is evidenced by the lack of uniformity in the various older descriptions of the pathology. However, in the exudative reactions in and about the atlanto-epistropheal joints there does exist this unstabilizing pathologic process in joints otherwise stable, which is an entity in itself and one that is as well recognized as the traumatic dislocations and fractures encountered in the lower cervical region. The unstable nature of these joints under conditions of mild stresses and trauma indicated by their capacity to subluxate and dislocate further typifies the mechanical setup in the spinal mechanism where ranges of mobility are great. In my experience at the New York Orthopedic and other hospitals I have found that in gentle head halter traction, at times assisted by manipulation, later supported by head helmet body jackets and removable collars, we have a fairly dependable and satisfactory form of treatment. This of course admits the tendency of these lesions to recur and the occasional failures that necessitate surgical fixation. Dr. Nicholson is offering an additional form of therapy which, if we choose, we may use safely in these cases and apparently a form of treatment that will succeed in some of the cases in which the other more recognized forms of treatment fail. While his series is small, his high percentage of successful reductions and their subsequent stability, as shown by adequate follow-up, speaks well for the method. He has noted some contraindications. Positive indications would seem to hinge around cases with lesions associated with chin decubitus, with mandible injury, painful cervical adenitis and parotitis, as well as among those cases that fail with traction and manipulation.

DR. BARBARA B. STIMSON, New York: Dr. Nicholson's paper has been most enjoyable. He has not been fair, however, to his own ingenuity to call his method a "spontaneous" reduction! Actually, the method is that of traction with the weight of the head exerting the pulling force on the cervical vertebrae by virtue of the described position. The spontaneity has been considerably assisted by the doctor. The series of cases has interested me greatly. I have not had the opportunity to study so many of the complete dislocations, and those I have seen, six in all, were all of traumatic origin. Of these two without fracture were reduced by manipulation. The others were all associated with fracture. One was reduced by traction on an air mattress, as described by Dr. Stookey, one by direct head traction, one was operated on and one refused operation, though reduction could not be maintained. He subsequently went on to spontaneous fusion in a partially corrected position. Over 250 cases of incomplete dislocation have been treated by head traction in the majority of instances. There are two questions I should like to ask. Dr. Nicholson says that his method is not applicable to early traumatic cases. How does he treat them? I feel strongly that the earliest possible reduction of dislocations and fractures is not only easiest but also does least damage to the adjacent soft parts. Surely he would not keep his patient on ice, as it were, until he felt it was safe to apply his method. I have been much troubled by nausea and vomiting in patients treated by traction, either by the Stookey method or by direct head pull. I would think that the extreme position described by Dr. Nicholson would tend to increase this discomfort, and I would like to ask him if this is so.

DR. JESSE T. NICHOLSON, Philadelphia: Dr. Stimson's inquiry as to why measures are not taken to reduce the dislocation at once should be qualified. It is not customary in Philadelphia any more than in New York to neglect the early treatment of the subjects. The delay is suggested before placing the head dependent, as this position might add to the local cord edema in the acute case. It therefore should not be tried until this complication is minimized. But two adults are included in the series. Both have developed pressure sores on the chin following several days traction with a Sayre collar. Nausea was a minor complaint in one adult. This subject, however, developed extensive edema of the scalp after the head hung three days. When the patient became ambulatory in a plaster cast, the edema subsided so that in four days it was necessary to apply another cast for adequate fixation of the head.

Clinical Notes, Suggestions and New Instruments

SULFATHIAZOLE URINARY CALCULI IN THE KIDNEYS, URETERS AND BLADDER

IN THE ABSENCE OF MARKED URINARY CHANGES FOLLOWING SULFATHIAZOLE THERAPY

SAMUEL A. LOEWENBERG, M.D., NORMAN G. SLOANE, M.D., AND PAUL CHODOFF, M.D., PHILADELPHIA

Sulfathiazole (2 sulfanilamide-thiazole) is the newest of the group of chemotherapeutic agents employed in the treatment of pneumococcic pneumonia. Its efficacy in pneumonia is being thoroughly investigated in many of the larger hospitals in this country. Clinical reports [1] and our own results show that in its therapeutic effects sulfathiazole in pneumonia compares favorably with sulfapyridine and that it is preferable to sulfanilamide. It also has the added advantage of being less toxic and less likely to cause some of the complications encountered after the use of either of these other drugs. Since sulfathiazole is still on trial it is important to record any of the complications or sequelae that may arise from its use. Reinhold, Flippin and Schwartz [2] observed that sulfathiazole is not as readily reabsorbed from the kidney tubules as are sulfapyridine and sulfanilamide. Gross, Cooper and Scott [3] reported the formation of sulfathiazole crystals in the distal collecting tubules of rats' kidneys after the administration of sulfathiazole. Pepper and Horack [4] reported the first instance of crystalline sulfathiazole concretions in the renal tubules of a patient treated for pneumonia with sulfathiazole. Our case is, to our knowledge, the second proved case of sulfathiazole renal concretions and the first in which there were no clinical signs of kidney inefficiency. Added interest in the case was the development of acute vegetative endocarditis and hepatic and splenic necrosis, which may be explained on the basis of the pneumococcemia and is not attributed to any toxic effect of the drug.

REPORT OF CASE

History.—H. S., a woman aged 49, was admitted to our service at the Philadelphia General Hospital March 29, 1940, with signs of left basal pneumonia.

She became ill March 17 with what was considered a cold or grip; her symptoms became progressively worse and she was sent to the hospital twelve days after the onset of her illness. On admission she complained of chills, pain in the chest, dyspnea, cough and hoarseness; there was blood-streaked expectoration.

Examination.—The patient was stout; she was thoroughly conscious and alert. The temperature was 102 F., the pulse rate 120 per minute and the respiratory rate 30 per minute. Her face was flushed; she had herpes labialis; the veins in her neck were distended and she was dyspneic.

The heart was enlarged and fibrillating, the heart rate being 160 per minute, and there was a suspicion of a murmur at

From the Medical Service of the Philadelphia General Hospital and the Jefferson Medical College of Philadelphia.

1. Flippin, F. H.; Schwartz, Leon, and Rose, S. B.: The Comparative Effectiveness and Toxicity of Sulfathiazole and Sulfapyridine in Pneumococcic Pneumonia, Ann. Int. Med. **13**: 2038 (May) 1940. Thornton, W. B.; Brown, W. H., and Wilson, J. S.: Clinical Toxicity of Sulfanilamide and Sulfapyridine, J. A. M. A. **114**: 1605 (April) 1940.

2. Reinhold, J. G.; Flippin, H. F., and Schwartz, Leon: Observations on the Pharmacology and Toxicology of Sulfathiazole in Man, Am. J. M. Sc. **199**: 393 (March) 1940.

3. Gross, P.; Cooper, F. B., and Scott, R. E.: Urol. & Cutan. Rev. **44**: 205, 1940.

4. Pepper, D. S., and Horack, H. M.: Crystalline Concretions in Renal Tubules Following Sulfathiazole Therapy, Am. J. M. Sc. **199**: 674 (May) 1940.

the mitral area which could not be timed because of the fibrillations. The blood pressure was 120 systolic, 80 diastolic.

The lungs showed evidence of lobar consolidation at the left base.

The abdomen was distended; the liver extended 11 cm. below the right costal margin; it was soft and its edge was rounded; the spleen was readily palpable. There was no ascites or superficial edema.

Sputum typed immediately after admission showed pneumococcus type XXV. The blood culture was positive within twenty-four hours for pneumococcus type XXV. Analysis of the blood showed hemoglobin content 68 per cent, erythrocytes 3,100,000, leukocytes 19,200, polymorphonuclears 80 per cent, lymphocytes 18 per cent, monocytes 2 per cent. The Wassermann and Kahn reactions of the blood were plus 4.

The first specimen of urine gave an acid reaction; specific gravity was 1.020; tests for albumin and sugar were negative; there were no casts; an occasional leukocyte was present.

Course in the Hospital.—Soon after admission, in addition to digitalis, she was given 3 Gm. each of sulfathiazole and sodium citrate, which dose was repeated in four hours; subsequently she received 1 Gm. each of sulfathiazole and sodium citrate every four hours until 25 Gm. had been given. April 1, the end of the fourth day, her temperature reached normal by lysis and she showed general improvement; at this time the administration of sulfathiazole was discontinued.

April 3 she had a relapse; the temperature rose to 103 F., the respiratory rate to 45 and the pulse rate to 120. She was extremely hoarse; the heart rate was regular and there was a loud systolic murmur audible over the entire precordium. The blood pressure was 130 systolic, 50 diastolic. The lungs showed an extension of the consolidation to a somewhat higher level on the same side. A profuse diarrhea developed and she became jaundiced. A second blood culture was positive for pneumococcus type XXV. Sulfathiazole and sodium citrate 1 Gm. each was ordered to be given every four hours, and she was placed in an oxygen tent. Her mind was clear.

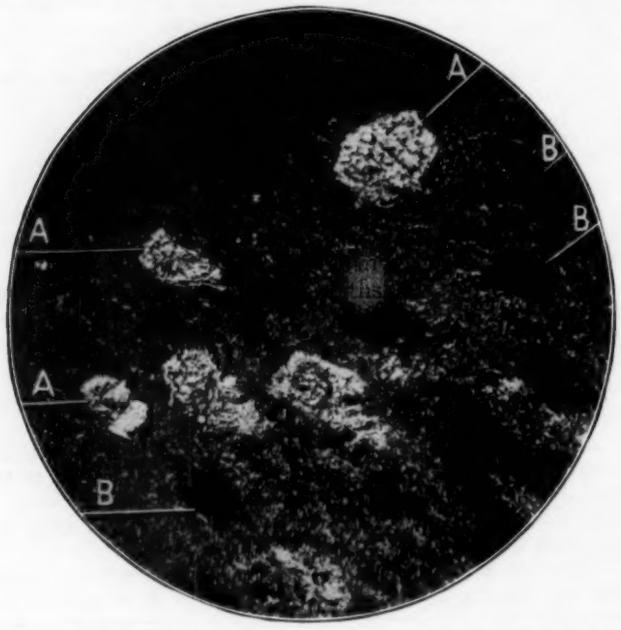

Fig. 1.—Frozen section of kidney showing acetylsulfathiazole concretions (*A*) and collecting tubules (*B*).

April 5, because of the pneumococcemia and endocarditis, a tentative diagnosis of acute bacterial endocarditis was suggested and the administration of 100,000 units of type XXV pneumococcus serum was attempted. Though she had not shown any serum sensitivity to the usual tests, a severe chill developed and the temperature rose to 105.4 F. (axillary) after only half of the 100,000 units had entered her vein. Further administration had to be discontinued.

April 6 she felt better; the temperature was 100 F. The lungs showed signs of resolution. The heart showed good compensation; the pulse rate was 100; there was a loud harsh systolic murmur over the body of the heart.

April 7 the temperature was 105.4 F., the pulse rate 152 and the respiratory rate 60. Her mentality was clear. There was

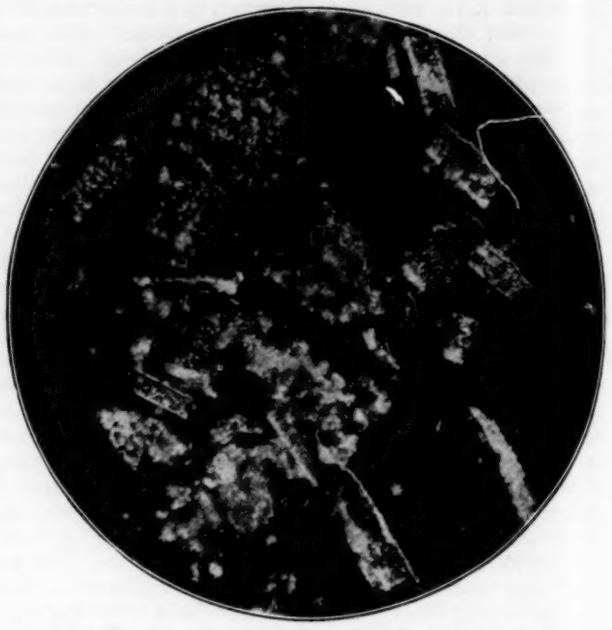

Fig. 2.—Microscopic appearance of crystals of acetylsulfathiazole taken from the concretions.

tubular breathing near the angle of the right scapula; the liver and spleen were very large; the patient, notwithstanding the dyspnea, seemed fairly comfortable.

April 8 there was no change in her general appearance or in her clinical manifestations. The heart rate was rapid and regular; sounds were muffled and the murmur was not audible. At 3 p. m. she suddenly died.

During the patient's entire stay in the hospital (ten days) she received, in addition to symptomatic treatment, 52 Gm. of sulfathiazole. Though the temperature reached normal on the fourth day, she had a relapse and remained acutely ill, distressingly dyspneic and quite cyanotic; these symptoms were not relieved in the oxygen tent or by other measures. The heart rate slowed and the rhythm became more regular under the influence of digitalis, but a loud systolic murmur developed over the body of the heart which was audible with equal intensity over the entire precordium. The blood pressure remained fairly constant between 126 systolic, 70 diastolic, to 130 systolic, 60 diastolic, and the day she died it was 130 systolic, 50 diastolic.

She was mentally alert until the last. At no time did she complain of urinary symptoms. Twenty-four hours before death the temperature rose to 105.4 F.; the heart murmurs disappeared and there was evidence of cardiac dilatation. Death was sudden.

The blood counts made during her stay in the hospital are given in table 1.

The blood Wassermann and Kahn tests gave a plus 4 reaction.

Blood urea was 19 mg. per hundred cubic centimeters on admission and 20 mg. several days later. Blood cholesterol was 118 mg. with 10 per cent esters. Blood sulfathiazole levels were from 5 to 7.6 mg. per hundred cubic centimeters.

Results of urinalyses are given in table 2.

Culture of the urine on April 3 gave negative results. The fluid intake and output were within normal proportion.

Culture of the feces on two occasions showed an unusual predominance of Staphylococcus aureus.

Autopsy was done by Dr. H. G. Schlumberger.

AUTOPSY

External Examination.—The body showed no cyanosis or edema. The skin had a slightly icteric tint but otherwise no abnormal pigmentation was noted.

Internal Examination.—Both pleural spaces were almost obliterated by dense fibrous bands; no free fluid was present. The peritoneal surfaces were smooth and glistening; the mesentery and omentum contained a great deal of fat. No free fluid was present in the peritoneal cavity, and the normal visceral relationships were preserved.

Pericardium: The surfaces were thin, smooth and glistening except for a 5 by 3 cm. area of opacity in the visceral layer covering the anterior part of the right ventricle. The usual amount of clear, pale yellow fluid was contained within the pericardial sac.

Aorta: The intima showed only a few small atheromatous plaques in the abdominal segment. The wall of the ascending aorta was moderately thickened and several white, waxlike plaques were seen on the intimal surface.

Heart: The myocardium was very flabby and uniformly soft and reddish brown. Both ventricles were slightly dilated; the auricles were filled with cruor. On the tricuspid leaflets, near the free margin there was a 1 by 1 cm. firm, friable, yellow mass closely adherent to the underlying valvular endocardium. The pulmonary valve showed no abnormalities. The mitral valve was thin, smooth, flexible and of average length, and there was nothing suggestive of vegetations. The papillary muscles were of average size; the chordae tendineae were not shortened or fused together. On the anterior cusp of the aortic valve there was a yellowish green, homogeneous, friable mass measuring 1.5 by 1 by 1 cm., which was firmly adherent to the ventricular surface of the valve. The remaining two cusps showed several firm white nodules measuring approximately 1 by 1 mm., arranged along the line of closure. The coronary vessels were free from any significant atherosclerosis.

Lungs: The consistency of both lungs was somewhat increased throughout but the left lower lobe was distinctly consolidated. The cut surfaces of the right lung and left upper lobe were hemorrhagic, and a great deal of blood tinged fluid escaped when pressure was made on the lung parenchyma. The left lower lobe on section was somewhat dry and more granular than the cut surfaces of the other lobes. The bronchial mucosa was hyperemic and edematous. The pulmonary vessels contained no thrombi. There was no evidence of suppuration in any portion of either lung. The regional lymph nodes were not remarkable.

Spleen: The spleen was greatly enlarged and so soft that on sectioning the pulp was almost semifluid. The capsule was thin, smooth and slate gray; the pulp was uniformly purplish red. The follicles and trabeculae could not be distinguished.

Kidneys: Both organs were moderately enlarged, of average firmness and cut with normal resistance. The capsules stripped with ease, revealing a smooth pale red surface. On section the cortex was found to be from 1 to 1.5 cm. in width, of a uniform pale red and indistinctly demarcated from the medulla. In the calices and pelves there were numerous bright orange colored irregular shaped calculi measuring from 1 to 2.5 mm. in diameter. The pelves were not dilated and the mucosa was uniformly smooth and moderately hyperemic.

Urinary Tract: The serosal surfaces were smooth and pale pink. The ureters were slightly dilated and contained numerous granules similar to those found in the calices. The left ureter near its source was almost completely occluded by a mass of the same type of orange colored calculi. The bladder was small and contracted; the mucosa was slightly hyperemic, and attached to its surface were several granular masses similar to those noted in the ureters and pelves.

TABLE 1.—*Blood Counts*

Date	Hemoglobin, per Cent	Red Blood Cells	White Blood Cells	Polymorphonuclears, per Cent	Staff Cells, per Cent	Segmented Forms, per Cent	Lymphocytes, per Cent	Monocytes, per Cent
3/31/40	68	3,100,000	19,200	80	..	..	18	2
4/ 1/40	68	3,320,000	16,400	76	64	12	12	12
4/ 3/40	68	3,200,000	18,400	92	82	10	8	
4/ 8/40	52	2,660,000	13,000	74	58	16	10	10

Genitalia: The uterus measured 5 by 6 by 3 cm.; it cut with the usual resistance. The endometrium averaged 2 mm. in thickness and was uniformly dark red. The fallopian tubes were tortuous, bound down by fibrous adhesions and in several places were moderately dilated. The ovaries were small, firm, white and fibrous.

Gastrointestinal Tract: The peritoneal surfaces were smooth and pale gray. The stomach contained a small amount of gray opaque fluid. The mucosa was smooth and pallid and showed numerous petechiae. The lumen of the large and small intestine was of average size and the contents were not abnormal. The mucosa was intact throughout and essentially normal in appearance. The mesenteric blood vessels showed no change.

TABLE 2.—*Urinalyses*

Date	Specific Gravity	Reaction	Albumin	Sugar	Microscopic Observations
3/31/40	1.020	Acid	Negative	Negative	Occasional leukocytes
4/ 5/40	1.016	Alkaline	Negative	Negative	Occasional leukocytes; occasional epithelial cells

Liver: This organ was enlarged, moderately soft and uniformly yellow. Resistance to cutting was somewhat decreased and the cut surface was uniformly pale yellow and soft with indistinct markings.

Gallbladder and Ducts: The gallbladder was slightly distended by 25 cc. of light amber colored bile which flowed readily through the ducts and from the ampulla of Vater. The wall was moderately thickened, and attached to the mucosa were numerous orange granules which in some places formed definite ridges. The bile ducts were not dilated and contained no calculi.

Pancreas: This organ was of average size, shape and consistency. It was a yellowish brown, firm and distinctly lobulated. The surrounding fat was of average amount and of the usual color. The pancreatic ducts appeared normal.

Adrenals: Both adrenals were of average size, shape and consistency. The medullary portions were a gray brown and firm. The cortical layers were dark brown instead of the usual deep yellow.

Vertebrae: The cancellous portion of the bodies contained uniformly pale red marrow.

Chemical Examination of the Concretions.—The kidney calculi on chemical examination were found to consist of acetylsulfathiazole to the extent of about 50 per cent of the dry weight. A slight trace of free sulfathiazole was present.[5]

SUMMARY AND COMMENT

Sulfathiazole concretions were found in the kidneys, ureters and bladder of a patient treated for pneumonia with sulfathiazole who did not present any evidence of disturbance of the urinary tract. It is therefore of clinical importance to study the effects of sulfathiazole on the kidneys so as to determine whether sulfathiazole crystals are nonirritating to the kidneys or whether there is a latent period between the formation of crystals in the urinary tract and the development of kidney insufficiency. If sulfathiazole crystals can remain in the kidneys, ureter and bladder without causing early clinical signs of renal damage, it will be desirable to determine its ultimate effect on the kidneys by studying the renal functions of patients, who were treated with the drug, for a period of one year after the drug has been discontinued.

Sulfathiazole in this case had no effect on the pneumococcemia or on the acute bacterial endocarditis.

How frequently crystallization of sulfathiazole may occur in the urinary tract is as yet unknown. Of sixteen autopsies reported by Flippin[6] on patients treated with sulfathiazole, none showed uroliths, though among the hundred or more patients treated with that drug there were quite a few who had mild urinary disturbances.

1905 Spruce Street.

5. This examination was by J. G. Reinhold, Ph.D., chief biochemist to the laboratory of the Philadelphia General Hospital.
6. Flippin, Harrison F.: Personal communication to the authors.

CONGENITAL HYPERTROPHY OF THE VERUMONTANUM

FREDERICK PILCHER JR., M.D., AND HAROLD W. PRICE, M.D.
CALGARY, ALTA.

Congenital hypertrophy of the verumontanum is one of the rarest lesions in the posterior urethra. A case in which this anomaly was discovered at autopsy led us to a thorough review of the literature, which disclosed only thirteen previously reported cases. In the case recorded here the lesion was somewhat different from any of those observed.

REPORT OF CASE

A. P. D., a white boy, was born at the Calgary General Hospital on July 2, 1937. This was the mother's second pregnancy. A previous and a subsequent child are both normal and well. Pregnancy and delivery were normal. The birth weight was 8 pounds 10½ ounces (3,926 Gm.). Routine physical examination after birth disclosed nothing abnormal. After the usual postnatal drop in weight the child began to gain normally. On the sixth day there were fever and diarrhea, but these lasted

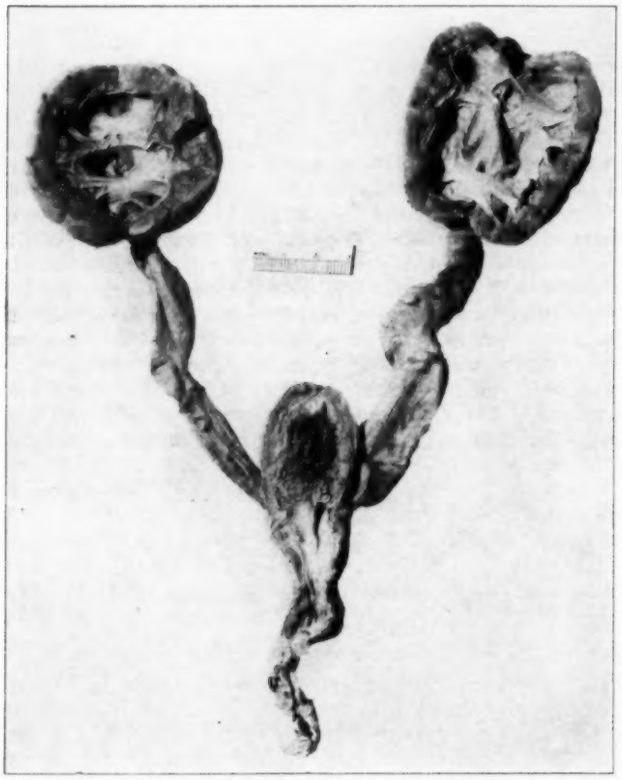

Fig. 1.—Entire urinary tract showing the dilated kidneys, tremendous dilatation of the ureter and thickened hypertrophy of the bladder.

only two days. Thereafter his progress was normal and uneventful. The child and mother left the hospital on the fourteenth day and went home to the country.

On July 22 the child was brought back to the city by his mother. He had nursed poorly, had not taken his bottle well and on the day of examination had refused to take anything by mouth. The child was markedly emaciated and moribund. The abdomen was soft and scaphoid, and peristaltic waves were visible. Both kidneys were easily palpable and larger than normal. Otherwise examination was negative. The child was sent to the hospital, where subcutaneous fluids were administered. He died five hours after admission.

Autopsy performed by Dr. Lola McLatchie showed marked emaciation and pale dry tissues. Complete examination was otherwise essentially negative except for the urinary tract. The illustrations show clearly the appearance of the fixed specimen. Both kidneys were full of thick purulent urine. The markedly enlarged and elongated verumontanum projected into the bladder. Lifted forward, the verumontanum acted as a valve which completely or almost completely occluded the urethra. There was no other obstruction in any part of the urethra.

From the Calgary Associate Clinic.

LITERATURE

The three congenital obstructive lesions observed in the posterior urethra are valves, contractures and hypertrophy of the verumontanum. According to the literature, valves are the

Fig. 2.—A clearer view of the elongated hypertrophied verumontanum.

most common and hypertrophy of the verumontanum the least common. Young, Frontz and Baldwin [1] in 1919 presented the first thorough review of congenital valves in the posterior urethra. Since then, painstaking reviews of the literature and reports of personal cases have been published by numerous authors. In none of these papers, however, is hypertrophy of the verumontanum mentioned as the sole cause of obstruction. In the presence of valves there often is observed a variable

Fig. 3.—Section through the elongated verumontanum and region of the bladder neck; reduced from a photomicrograph with a magnification of 9 diameters.

degree of enlargement or distortion of the verumontanum, but the valves act as the obstructing agent. Enlargement of the verumontanum alone as the cause of obstruction was first

1. Young, H. H.; Frontz, W. A., and Baldwin, J. C.: Congenital Obstruction of the Posterior Urethra, J. Urol. 3: 289-354 (Oct.) 1919.

reported by Bugbee and Wollstein[2] in 1923. They observed seven cases at autopsy and one clinical case. All but two of the patients were under 1 year of age and the oldest was 3½ years. Robinson[3] in 1927 reported an autopsy specimen from a man aged 19. Dodson and Lorraine[4] observed during life a youth aged 19 in whom hypertrophy of the verumontanum was a cause of urinary obstruction and retention, and a good result followed fulguration of the verumontanum. Baldridge[5] reported another case in which cure followed fulguration of the verumontanum in an 11 year old patient. Somerford[6] in 1936 again observed this lesion at autopsy in a child aged 11 years. The latest report is that of Grant[7] in 1938 in which he mentions a boy aged 13 years in whom hypertrophy of the verumontanum was noted during life and relief of obstruction followed fulguration of the verumontanum.

COMMENT

There is no satisfactory explanation for congenital hypertrophy of the verumontanum. The greatly enlarged verumontanum probably acts as a ball valve just in front of the external sphincter in the same way that median lobe prostatic hypertrophy acts in the region of the internal sphincter. Mechanical obstruction to the flow of urine is produced.

The pathologic changes in the urinary tract and the symptoms are similar to those resulting from enlargement of the prostate gland or any other type of infravesical obstruction. There is dilatation of the posterior urethra behind the verumontanum. During the earlier stages of obstruction there are hypertrophy of the bladder with trabeculation, hypertrophy of the trigon, perhaps diverticulum formation and inflammation, dependent on the degree of associated infection. Later, when decompensation of the bladder occurs, there follows dilatation of the bladder, which together with inflammatory changes in the bladder wall result in incompetence of the ureterovesical valve mechanism. Ureteral and pelvic dilatation occur, and in the most advanced cases the renal parenchyma becomes a thin shell. This compression atrophy, accompanied in many cases by infection, eventually reduces renal function to a point at which it will no longer support life.

The early symptoms are those of urinary obstruction. Later there are renal insufficiency and uremia. Frequency of urination is the most common symptom. With associated infection, frequency often becomes very marked with almost constant dribbling. Enuresis may be the most prominent symptom. One may observe in older children considerable straining, hesitancy and difficulty in voiding. When bladder distention occurs it may be observed as a mass in the lower part of the abdomen. Recurrent episodes of fever, often diagnosed as pyelitis, are common. As renal damage advances, the symptoms of renal insufficiency appear. There may be failure to gain, or even loss of weight. Loss of appetite and gastrointestinal upsets are common, as well as headaches and lassitude. With a lowered renal reserve these patients are more susceptible to intercurrent infections and often die of them. They may lapse into uremic coma. The true cause of the trouble may never be suspected, and the patient is often treated for pyelitis or chronic nephritis.

The diagnosis is established by making thorough urologic examination of all children who have chronic urinary troubles. Urethroscopic examination of these children will differentiate contractures, valves, hypertrophy of the verumontanum and cord bladder.

The treatment consists in removal of the obstruction when the condition of the patient permits. Infection and renal impairment may necessitate preliminary urethral catheter or suprapubic drainage for a variable length of time. Abundant fluids and urinary antiseptics will hasten improvement. Blood transfusion is indicated in the anemic and those in generally poor condition. The hypertrophied verumontanum may be destroyed by any of the various punch instruments or by simple fulguration through the cysto-urethroscope.

SUMMARY

The congenital hypertrophy of the verumontanum here reported is of unusual configuration. This is one of the rarest obstructive lesions in the posterior urethra. A thorough review of the literature discloses only thirteen previously recorded cases. With careful attention to urinary symptoms and thorough urologic examination, this lesion should be discovered before renal damage has progressed to a point at which recovery is impossible. Treatment consists in proper preoperative preparation of the patient, followed by transurethral punch or fulguration of the verumontanum.

214 Sixth Avenue West.

2. Bugbee, H. G., and Wollstein, Martha: Retention of Urine Due to Congenital Hypertrophy of the Verumontanum, J. Urol. **10**: 477-490 (Dec.) 1923.
3. Robinson, W. W.: Congenital Hypertrophy of the Verumontanum as a Cause of Urinary Retention, J. Urol. **17**: 381-390 (March) 1927.
4. Dodson, A. I., and Lorraine, Helen: Congenital Obstruction of the Posterior Urethra, Virginia M. Monthly **58**: 102-107 (May) 1931.
5. Baldridge, R. R.: A Case of Congenital Hypertrophy of the Verumontanum, New England J. Med. **213**: 46-49 (July 11) 1935.
6. Somerford, Anne E.: Congenital Urethral Obstruction, Lancet **1**: 1473 (June 27) 1936.
7. Grant, Owsley: Obstructions at the Vesical Neck in Children, J. Urol. **40**: 114-120 (July) 1938.

Special Article

GLANDULAR PHYSIOLOGY AND THERAPY

CORTICOTROPIC (ADRENOTROPIC), THYROTROPIC AND PARATHYROTROPIC FACTORS

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This special article is published under the auspices of the Council on Pharmacy and Chemistry. It is one of a series which will be published in book form as the second edition of "Glandular Physiology and Therapy." The opinions expressed in this article are those of the author and do not necessarily represent the views of the Council.—ED.

THE CORTICOTROPIC FACTOR

It is to be noted that the word "corticotropin" (or "corticotrophin") is now being widely used as a descriptive term for the principle in the anterior lobe of the pituitary gland hitherto commonly spoken of as the adrenotropic factor. This is in line with the general recommendations of the Third International Conference on the Standardization of Hormones.[1]

Physiologic Significance of Corticotropin.—There is now a mass of evidence that the maintenance of the cortex of the adrenal gland, in the morphologic as well as the functional sense, is dependent on the secretory activity of the normal anterior lobe of the pituitary. The atrophic adrenals of the completely hypophysectomized animal are not entirely functionless, however, since removal of them from rats hypophysectomized some weeks previously is not tolerated, and death ensues quickly. The function of the corticotropic factor is therefore to maintain the normal structure and function of the adrenal cortex.

Nature of the Corticotropic Factor.—Until such time as the hormones secreted by the anterior lobe are obtained in pure form, it will be impossible to know positively whether the substance acting on the adrenal cortex is a single substance having only this specific hormonal activity or a substance having other physiologic effects, tropic or otherwise, in addition to the

From the Department of Biochemistry, McGill University.
1. Report of the Third International Conference on the Standardisation of Hormones, Bull. Health Organ. League of Nations **7**: 887-899 (Oct.) 1938.

corticotropic property. Collip[2] reported that an isoelectric protein fraction obtained from an acid acetone extract had the properties of three hormones of the anterior lobe, namely, the growth-promoting factor, corticotropin and prolactin. The corticotropic activity of such extracts was shown to be fairly resistant to heating over a wide p_H range; the greatest stability was shown at p_H 3 to 5. Moon,[3] using the Lyons method[4] for the preparation of prolactin, showed that the material insoluble at p_H 6.5 is rich in corticotropin. This fraction had little prolactin activity, whereas a fraction obtained by isoelectric precipitation at p_H 5.5 was rich in prolactin but had a lower corticotropic content. It can be positively stated that corticotropin is separate and distinct from thyrotropin and from gonadotropin.[5] All available evidence points to corticotropin being of protein nature.

Preparation of Potent Extracts of Corticotropin.—Although it has been my experience that most protein fractions obtained from extracts of anterior lobes have more or less corticotropic activity, I have found the following method satisfactory for the preparation of an extract rich in corticotropin and having a minimum of other principles of the anterior lobe.

Prime fresh tissue which has been largely defatted and dehydrated by extraction with alcohol is extracted twice with 5 volumes of 0.25 per cent acetic acid for each volume of original gland tissue used. The residues are then extracted a third time with 5 volumes of 0.25 per cent acetic acid, the mixture being heated to 75 C. for fifteen minutes, then cooled and filtered. The tissue residues are then suspended in 5 volumes of 0.25 per cent acetic acid and placed in a boiling water bath for four to six hours, the mixture being frequently stirred. The mixture is then filtered, and the filtrate is concentrated at low temperature and pressure until the volume is equal to the original volume of gland used. Sufficient concentrated hydrochloric acid is then added to make a 0.25 per cent concentration of this reagent, and the acidified mixture is placed in a boiling water bath for twelve hours. The extract at this stage is adjusted to p_H 4 and is ready for assay on the hypophysectomized rat. The salt content can be reduced by a short dialysis in cellophane. Fractionations of such extracts with a view to obtaining the corticotropic principle in purer form are being undertaken. An earlier observation that extracts obtained from simple hydrolysates of pituitary tissue (treatment on a boiling water bath for twelve to twenty-four hours with 10 volumes of 0.25 per cent hydrochloric acid) produced a number of physiologic effects when tested in the appropriate manner suggested the process described here for the preparation of extracts of corticotropin. In addition to retaining corticotropic properties, these simple hydrolysates were found to contain appreciable amounts of the metabolic, glycotropic and ketogenic substances. Feeding of hypophysectomized rats with such potent preparations has given no evidence that the corticotropic substance is active when taken orally.

Bioassay for the Corticotropic Substance.—In my opinion the most satisfactory method of assay for corticotropin is by the use of hypophysectomized rats. These animals should not be used until an adequate time has elapsed after hypophysectomy to insure that cortical atrophy has progressed to a marked degree. One month is a safe interval. In the method of assay originally described,[6] one adrenal was removed from the test animal prior to beginning injections of the extract to be assayed. This was weighed and sectioned, and served as the control. The injections were made twice a day for six days, and then the remaining adrenal was removed, weighed and sectioned for histologic study. It was suggested that a 50 per cent increase in weight together with positive histologic evidence of cortical repair should be considered a unit effect. A more extensive study of the response of hypophysectomized rats to a single corticotropic preparation administered at increasing levels of dosage showed that the accurate assay of such extracts for corticotropin is a very difficult matter.[7] It is now believed that much greater uniformity can be obtained if restoration to normal or nearly normal size of the adrenals is accepted as a unit effect. It is suggested also that the period of injections be increased to ten days, that several animals be used and that biopsy is unnecessary.

The method of Moon[3] for the assay of corticotropin consists in the treatment of normal 21 day old male rats for three days with the extract to be tested. Moon defined a unit as that amount of extract tested in this manner which caused a fifty per cent increase in the weight of the adrenals. An inert protein solution is used as a control in the Moon test. The Moon method of assay has much to commend it, and in the case of purified extracts there should be little danger of nonspecific effects being obtained, for it is well known that adrenal enlargement due to cortical hypertrophy is readily obtained by treatment of normal rats with injections of a foreign protein.

General Considerations.—The ability of the normal anterior lobe to secrete corticotropin quickly in increased amounts in response to a great variety of so-called nonspecific agents would seem to constitute one of the chief arms of defense on the part of the body to injurious stimuli.[8] As yet no success has been had in the demonstration of corticotropin in the blood. It would be of clinical value if more sensitive methods for the detection of this substance were available, so that actual assays of blood and urine in cases of Cushing's disease could be made.

No specific clinical value for preparations containing corticotropin has been demonstrated. There is the possibility that they might be of definite prophylactic value in cases of anticipated shock. There is likewise the possibility that in certain cases of Addison's disease there might be benefit from this form of therapy. Presumably, although there is no direct proof of it, the corticotropic substance causes the adrenal cortex to function to the full measure of its capacity. I have observed that the activity of hypophysectomized rats as measured in the running wheel cage is greatly increased after prolonged treatment with corticotropic extract. In view of the important, though as yet none too well defined, role which the adrenal glands play in carbohydrate and protein metabolism, as well as other phases of metabolism, a very important place must be assigned to the corticotropic hormone among the family of active principles of the anterior lobe.

THE THYROTROPIC HORMONE

Since the publication of the last edition of "Glandular Physiology and Therapy," in which knowledge of the thyrotropic hormone was reviewed, numerous papers have appeared dealing with this subject, but, as Van Dyke remarked in his excellent review of the physiology and pharmacology of the pituitary gland,[9] recent investigations of the thyrotropic hormone from various biologic standpoints have yielded a disappointingly small crop of facts. Much of the effort has been expended in consolidating or extending slightly knowledge which was already available.

2. Collip, J. B.: Properties of Anterior Lobe Extracts, in Cold Spring Harbor Symposia on Quantitative Biology, Cold Spring Harbor, L. I., New York, 1937, vol. 5, pp. 210-217.

3. Moon, H. D.: Preparation and Biological Assay of Adrenocorticotropic Hormone, Proc. Soc. Exper. Biol. & Med. **35**: 649-652 (Jan.) 1937.

4. Lyons, W. R.: Preparation and Assay of Mammotropic Hormones, Proc. Soc. Exper. Biol. & Med. **35**: 645-648 (Jan.) 1937.

5. Collip, J. B.; Anderson, E. M., and Thomson, D. L.: The Adrenotropic Hormone of the Anterior Pituitary Lobe, Lancet **2**: 347 (Aug. 12) 1933.

6. Collip, J. B.: Some Recent Advances in the Physiology of the Anterior Pituitary, J. Mt. Sinai Hosp. **1**: 28-71 (May-June) 1934. Collip.[5]

7. Collip, J. B.: Results of Recent Studies on Anterior Pituitary Hormones, Edinburgh M. J. **45**: 782-804, 1938.

8. Selye, Hans: Thymus and Adrenals in the Response of the Organism to Injuries and Intoxications, Brit. J. Exper. Path. **17**: 234-248 (June) 1936.

9. Van Dyke, H. B.: The Physiology and Pharmacology of the Pituitary Body, Chicago, University of Chicago Press, 1939, vol. 2.

Heyl and Laqueur [10] expressed the view that the principle responsible for thyroid enlargement differs from that which causes the histologic signs of hyperplasia. Heyl [11] emphasized that certain pituitary extracts cause obvious histologic signs of thyroid stimulation without increasing the weight of the gland, while other extracts elicit a pronounced increase in weight. He isolated a protein-free acetone-soluble pituitary fraction which had no effect on the thyroid by itself but caused marked enlargement of the gland when given in combination with a highly purified thyrotropic preparation that in itself caused only histologic signs of hyperplasia. He concluded that, in addition to the thyrotropic hormone, the hypophysis produces an activator responsible for the increase in weight. More recently, Billingsley,[12] studying this question in my laboratory, summarized his results as follows:

A number of thyrotropic extracts have been simultaneously assayed by the weight and histology of the guinea pig thyroid, and by the metabolic rate. No correlation can yet be expressed between these, except that increase in weight and hyperplasia apparently are associated more often than are either of these responses with an increased metabolism. The metabolic rate was found to respond most readily to thyrotropic extracts, and the guinea pig was more sensitive than the hypophysectomized rat. The anterior pituitary appears to have a two-fold action on the thyroid: one which influences the secretion of the thyroid hormone, the other to change the morphology of the gland. It is doubtful whether an identical mechanism is involved in each case, as indicated by comparative studies of the three assay methods.

Relations of the Thyrotropic Hormone to Other Hypophysial Principles.—Riddle and his co-workers [13] showed that active gonadotropic pituitary preparations tested in pigeons do not always exert a thyrotropic effect. This indicates that the two hormones are not identical. Yet more recently, Tolksdorf and Jensen [14] and Jensen and Tolksdorf [15] came to the conclusion that the thyrotropic factor is identical with the interstitial cell–stimulating, or luteinizing, factor, since all pituitary fractions containing thyrotropin proved also to be active luteinizers and vice versa. Since purified thyrotropic preparations do not inhibit the action of insulin in the mouse, Jensen and Grattan [16] concluded that the glycotropic action is not due to the thyrotropic principle, thus confirming the view of Young.[17]

Mechanism of the Thyrotropic Action.—Schneider [18] and Schneider and Widmann [19] observed that in the dog an extract containing thyrotropin increases the iodine content of the blood without a period of latency, thus differing from the action of thyroxin. Similarly in the guinea pig it leads to a rapid appearance of signs of thyrotoxicosis. Although these signs are not evident before the thyroid undergoes hyperplasia, they develop much sooner than after treatment with thyroxin. These experiments suggest that the actions of the thyrotropic principle cannot be regarded as due merely to a liberation of thyroxine.

The fact that the thyrotropic hormone acts directly on the thyroid without any intermediary has been demonstrated by Eitel and his associates,[20] who found that an extract containing this factor when added to slices of dog thyroid increased the consumption of oxygen by the thyroid tissue and caused histologic changes similar to those usually seen in vivo.

Bioassay for the Thyrotropic Substance.—The Third International Conference on the Standardization of Hormones [1] agreed that extracts of the thyrotropic factor should be assayed in comparison with an international standard preparation which is distributed by the National Institute for Medical Research, Hampstead, London, England; 250 micrograms of this preparation are equivalent to 1 unit. It also agreed that only those tests can be considered safe which are based on actual observation of a stimulation of the thyroid, since other effects may be due to impurities in the extract.

In the axolotl, preparations of the thyrotropic substance induce metamorphosis, and this effect has been suggested as a basis for the assay of extracts for the thyrotropic principle.[21]

The frog tadpole has been used for the assay of preparations for the thyrotropic substance by Cuyler and co-workers,[22] who standardized such preparations on the basis of an accelerating effect on metamorphosis.

The grass snake (Tropidonotus natrix) is a particularly good test object, according to Mason,[23] because its thyroid, unlike those of laboratory rodents, shows surprisingly little variation from the normal resting condition unless stimulated by pituitary extracts. The disadvantage of this method is that few laboratories are equipped with this experimental material.

The thyroid of the pigeon or of the dove likewise undergoes pronounced enlargement and shows histologic signs of hyperplasia after administration of an extract containing thyrotropin and is a suitable test object for assay purposes. It is important, however, to use either immature [24] or hypophysectomized [25] birds in order to make sure that the untreated controls have resting thyroids.

Immature chicks were first employed for such bioassays by Stimmel and associates,[26] who considered the decrease in the iodine content of the thyroid caused by the thyrotropin in an extract as an indicator of activity. Later Smelser [27] and Cope [28] used the increase in the weight and the histologic signs of hyperactivity elicited by the thyrotropic factor in the 1 day old chick as a basis for bioassay. Kabac and Liapin [29] made an accurate detailed study of this test object, using 5 to 6 day old chicks and estimating thyrotropic potency merely by the increase in thyroid weight. They stated: "As an arbitrary unit of thyrotropic preparation we designate the amount which brings

10. Heyl, J. G., and Laqueur, Ernst: Zur quantitativen Bestimmung der thyreotropen Wirkung von Hypophysenvorderlappenpräparaten und die Einheit des thyreotropen Hormons, Arch. internat. de pharmacodyn. et de thérap. **49**: 338-354 (Jan. 15) 1935.
11. Heyl, J. G.: Thyreotropes Hormon und Wachstum der Schilddrüse, Acta brev. Neerland. **4**: 102, 1934.
12. Billingsley, L. W.: Factors Affecting the Metabolism of Small Animals, Thesis, McGill University Graduate School, 1937.
13. Riddle, Oscar; Bates, R. W., and Dykshorn, S. W.: Thyroid Hypertrophy as a Response to the Gonad-Stimulating Hormone of the Pituitary, Proc. Soc. Exper. Biol. & Med. **30**: 794-797 (March) 1933.
14. Tolksdorf, Sybylle, and Jensen, H.: Mechanism of Pituitary Gonadotropic Antagonism, Proc. Soc. Exper. Biol. & Med. **42**: 466-469 (Nov.) 1939.
15. Jensen, H., and Tolksdorf, Sybylle: The Relation Between the Interstitial-Cell-Stimulating and Thyrotropic Effects of the Anterior Pituitary, J. Biol. Chem. **133**: xlix-l (May) 1940.
16. Jensen, H., and Grattan, J. F.: The Identity of the Glycotropic (Anti-Insulin) Substance of the Anterior Pituitary Gland, Am. J. Physiol. **128**: 270-275 (Jan.) 1940.
17. Young, F. G.: The Identity and Mechanism of Action of the Glycotropic (Anti-Insulin) Substance of the Anterior Pituitary Gland, Biochem. J. **32**: 1521-1539 (Sept.) 1938.
18. Schneider, E.: Morbus Basedow und künstliche Steigerung der Schilddrüsentätigkeit, Arch. f. klin. Chir. **173**: 421-428, 1932.
19. Schneider, E., and Widmann, E.: Klinische und experimentelle Untersuchungen zum Problem des Kropfes und der Basedowschen Krankheit: III. Mitteilung, Deutsche Ztschr. f. Chir. **238**: 206-215, 1932.
20. Eitel, Hermann; Krebs, H. A., and Loeser, Arnold: Hypophysenvorderlappen und Schilddrüse: Die Wirkung der thyreotropen Substanz des Hypophysenvorderlappens auf die Schilddrüse in vitro, Klin. Wchnschr. **12**: 615-617 (April 22) 1933.
21. Spaul, E. A.: Experiments on the Injection of Pituitary Body (Anterior Lobe) Extracts to Axolotls, Brit. J. Exper. Biol. **2**: 1, 1924.
22. Cuyler, W. K.; Stimmel, B. F., and McCullagh, D. R.: Quantitative Studies with Thyrotropic Hormone, J. Pharmacol. & Exper. Therap. **58**: 286-293 (Nov.) 1936.
23. Mason, E. M.: Assay of Thyrotropic Hormone, Nature, London **142**: 480-481 (Sept. 10) 1938.
24. Riddle, Oscar: Studies on Pituitary Functions, Endocrinology **15**: 307-314 (July-Aug.) 1931.
25. Miller, R. A., and Riddle, Oscar: Stimulation of Adrenal Cortex of Pigeons by Anterior Pituitary Hormones and by Their Secondary Products, Proc. Soc. Exper. Biol. & Med. **41**: 518-522 (June) 1939.
26. Stimmel, B. F.; McCullagh, D. R., and Picha, Valerian: The Thyrotropic Hormone of the Pituitary Gland and Iodine Metabolism, J. Pharmacol. & Exper. Therap. **57**: 49-55 (May) 1936.
27. Smelser, G. K.: Assay of Thyrotropic Hormone on Day-Old Chicks, Proc. Soc. Exper. Biol. & Med. **37**: 388-390 (Nov.) 1937; Chick Thyroid Responses as a Basis for Thyrotropic Hormone Assay, Endocrinology **23**: 429-438 (Oct.) 1938.
28. Cope, C. L.: The Young Chick as Test for the Thyrotropic Hormone, J. Physiol. **94**: 358-364 (Dec.) 1938.
29. Kabac, J. M., and Liapin, N. I.: A Quantitative Study of the Thyrotropic Action of Extracts of Anterior Pituitary on Chicks., Bull. de biol. et de méd. expér. de l'U. R. S. S. **5**: 334-338 (April) 1938.

the weight of both thyroids of the chick to 8 mg. (on the average) after daily subcutaneous injections during five days. The experiments were carried out on 5 day old chicks, and autopsy was performed one day after the last injection." Bergman and Turner,[30] who employed the 1 day old white leghorn chick, emphasized that males are more sensitive than females. They defined the unit of thyrotropic activity as the total amount of extract administered subcutaneously once daily during four days which will cause a mean increase of 50 per cent (to about 5.4 ± 0.26 mg.) in thyroid weight in 20 chicks whose body weights average 55 ± 10 Gm. This unit corresponds to about one quarter of the guinea pig unit employed by the same investigators.

The guinea pig is the most commonly employed test object for thyrotropin. It represents an excellent test object, but a relatively young animal must be used in order to insure that the thyroid is in the resting stage before the thyrotropic preparation is administered. Aron [31] and Aron and Klein [32] stated that this is always the case in animals weighing less than 250 Gm. Loeser [33] used guinea pigs weighing 180 to 220 Gm. However, several subsequent investigators found that even in the small animal the thyroid may show signs of hyperplasia and of absorption of colloid under apparently normal conditions.[34] This variability of the normal thyroid structure induced Benazzi [35] and Junkman and Schoeller [36] to employ only animals weighing between 100 and 150 Gm. Aron [37] insisted, however, that the 200 Gm. guinea pig is suitable for assay purposes. He defined the unit as 1/100 of the amount necessary to produce a 50 to 100 per cent weight increase in the thyroid of a 200 Gm. guinea pig twenty-four hours after this amount is administered in a single injection. Histologically, 100 units causes absorption of colloid and secretory phenomena in the enlarged acinous cells throughout the glandular parenchyma. Ten units exerts such an effect only in the central portion of the gland; 40 to 45 units represents the amount which is most easily gaged in a single test since it causes absorption of colloid, hyperplasia and the appearance of mitotic figures, but none of these signs is sufficiently marked to make it impossible to differentiate the effect from that of still higher doses. Well aware of the variability of the thyroid even among young normal guinea pigs, Paal and Kleine [38] described a "resting diet" which causes the thyroid to become entirely free of any signs of activity and thus makes it particularly suitable for bioassay purposes. De Fremery [39] advocated pretreatment with the thyroid depressing diiodotyrosine for the same reason. Krogh and associates [40] emphasized that a few vacuoles in the colloid of the thyroid gland cannot be considered as significant, and this is in agreement with my own observations. However, if this is kept in mind, 200 Gm. guinea pigs are quite suitable for assay purposes, unless extremely small doses have to be detected. Such guinea pigs have also been used by Rowlands and Parkes,[41] who adopted as a unit "the thyrotropic activity contained in an amount of extract which given daily for 5 days will cause the thyroids of the 200 Gm. guinea pigs to attain a weight of 60 mg., i. e., about double the normal." This method of assay has been accepted by Junkman and Loeser.[42] Starr and Rawson,[43] Rawson and Starr [44] and Starr and others [45] measured the height of the thyroid epithelium and found it to be about 3.75 microns in normal females weighing 180 to 225 Gm. Using this "microhistometric" method, they assayed urine for its thyrotropic activity in various diseases by the increase in epithelial height which it produces. Heyl and Laqueur [10] insisted that the histologic changes, namely, the increase in the epithelial height and the vacuolation of the colloid, are the only satisfactory indexes of thyrotropic activity. They worked out a scale of six different stages of histologic signs of activity which they designated by the letters p to u. They termed "borderline dose" the amount which when given in two intraperitoneal injections on two consecutive days will cause in two thirds of the treated 150-200 Gm. guinea pigs a reaction "s" in the middle part of the thyroid within forty-eight hours. This reaction "s" is defined as a thickening of the cells in which the nucleus becomes round and the protoplasm develops on the distal pole of the cell to about the width of the diameter of the nucleus. In order to keep their unit as close as possible to those generally in use, they defined 1 guinea pig unit as one quarter of the "borderline dose." Wilcke [46] pointed out that it is important always to use the same fixative, since Susa's—which causes practically no shrinkage—makes the cells appear higher than does ordinary solution of formaldehyde U. S. P. diluted 1:10. He claimed that for the Heyl and Laqueur test the latter fixative is preferable. More recently Bergman and Turner [30] defined 1 guinea pig unit as the total amount of an extract containing the thyrotropic factor which when administered subcutaneously once daily on five successive days causes a mean increase of 50 per cent (to about 26.4 ± 1.63 mg.) in the thyroids of 10 male guinea pigs whose weights average 155 ± 15 Gm. According to Bastenie and Zylberszac,[47] 0.025 mg. of colchicine given for every 30 Gm. of body weight to 220-250 Gm. guinea pigs makes the mitogenetic action of the thyrotropic extract readily detectable, since colchicine arrests mitotic division in the metaphase. This drug should be administered about nine hours before killing the animals.

The decrease in the iodine content of the thyroid furnishes another test of thyrotropic activity in guinea pigs.[48]

The thyroid of the mouse is generally not considered to be a suitable test object for bioassay purposes, although Paal and Kleine [38] claimed that by using a special diet one may sufficiently repress the thyroid even in this species to make the effect of thyrotropic evident.

The thyroid of the rat is normally too variable to be useful for bioassay purposes. In hypophysectomized animals, on the other hand, the restoration of the atrophic epithelium gives a good index for thyrotropic activity.[49] The low basal metab-

30. Bergman, A. J., and Turner, C. W.: A Comparison of the Guinea Pig and Chick Thyroid in the Assay of the Thyrotropic Hormone, Endocrinology **24**: 656-664 (May) 1939.

31. Aron, Max: (*a*) Action de la préhypophyse sur la thyroïde chez le cobaye, Compt. rend Soc. de biol. **102**: 682-684 (Nov. 29) 1929; (*b*) Particularités histologiques de la réaction de la thyroïde aux extraits de lobe antérieur d'hypophyse, ibid. **103**: 145-147 (Jan. 24) 1930; (*c*) L'hormone préhypophysaire excito-sécrétrice de la thyroïde, Contribution à l'étude du fonctionnement thyroïden, Rev. franç. d'endocrinol. **8**: 472-520 (Dec.) 1930; (*d*) Note de technique sur la mise en évidence et évaluation quantitative des faibles taux de "thyréo-stimuline" préhypophysaire présents dans le sang ou l'urine, Compt. rend. Soc. de biol. **109**: 218-220 (Jan. 29) 1932.

32. Aaron, Max, and Klein, M.: Sur la présence, dans l'urine humaine, d'une substance douée de la même action sur la thyroïde que l'extrait préhypophysaire, et sur l'interprétation de la réaction de diagnostic de la grossesse, Compt. rend. Soc. de biol. **103**: 702-704 (March 7) 1930.

33. Loeser, Arnold: Die Darstellung thyreotrop wirksamer Extrakte aus Hypophysenvorderlappen, Arch. f. exper. Path. u. Pharmakol. **166**: 693-702, 1932.

34. del Castillo, E. B., and Magdalena, A.: Hypophyse et thyroïde. Pouvoir excito-thyroïdien du sérum sanguin, Compt. rend. Soc. de biol. **108**: 917-918 (Dec. 4) 1931. del Castillo, E. B.: Hypophyse et thyroïde: La thyroïde les jeunes cobayes comme réactif pour déceler l'activité thyréostimulatrice du sérum, ibid. **111**: 461-464 (Nov. 4) 1932.

35. Benazzi, M.: Sul test di Aron per la tireostimolina preipofisaria, Boll. Soc. ital. di biol. sper. **8**: 1212, 1933.

36. Junkman, Karl, and Schoeller, Walter: Ueber das thyreotrope Hormon des Hypophysenvorderlappens, Klin. Wchnschr. **11**: 1176-1177 (July 9) 1932.

37. Aron, Max: Sur le titrage biologique de la thyréo-stimuline préhypophysaire: Le "seuil des mitoses" dans la thyroïde des cobayes traités, Compt. rend. Soc. de biol. **123**: 250-253, 1936.

38. Paal, Hermann, and Kleine H. O.: Ueber die Abhängigkeit der Schilddrüsen-funktion von alimentären und hormonalen Faktoren, Beitr. z. path. Anat. u. z. allg. Path. **91**: 322-342, 1933.

39. de Fremery, P.: Die Wirkung des Dijodtyrosins auf die Rattenschilddrüse, Acta brev. Neerland. **5**: 35-36, 1935.

40. Krogh, Marie; Lindberg, Anna-Louise, and Okkels, Harald: Studies on the Thyroid Gland: III. Experimental Hyperactivity of the Thyroid Gland, Acta path. et microbiol. Scandinav. **9**: 37-54, 1932.

41. Rowlands, I. W., and Parkes, A. S.: Quantitative Study of the Thyrotropic Activity of Anterior Pituitary Extracts, Biochem. J. **28**: 1829-1843 (May) 1934.

42. Junkman, Karl, and Loeser, Arnold: Die Wertbestimmung des thyreotropen Hormons der Hypophyse, Arch. f. exper. Path. u. Pharmakol. **188**: 474-488, 1938.

43. Starr, Paul, and Rawson, R. W.: Graphic Representation of Thyroid Response to Stimulation by Thyrotropic Hormone, Proc. Soc. Exper. Biol. & Med. **35**: 603-605 (Jan.) 1937.

44. Rawson, R. W., and Starr, Paul: Direct Measurement of Height of Thyroid Epithelium: A Method of Assay of Thyrotropic Substance; Clinical Application, Arch. Int. Med. **61**: 726-738 (May) 1938.

45. Starr, Paul; Rawson, R. W.; Smalley, R. E.; Doty, Ellis, and Patton, Helen: The Microhistometric Method Applied to Thyrotropic Hormone Assay, West. J. Surg. **47**: 65-75 (Feb.) 1939.

46. Wilcke, J.: Einfluss der Fixierung auf das histologische Bild der Schilddrüse bei Meerschweinchen, Acta brev. Neerland. **5**: 99, 1935.

47. Bastenie, P., and Zylberszac, S.: Mise en évidence de stimulations hormonales par la colchicine. Détection de stimulation thyroïdienne par l'extrait antéhypophysaire, Compt. rend. Soc. de biol. **126**: 446-448, 1937.

48. McCullagh, D. R., and Stimmel, B. F.: A Biochemical Method for the Assay of the Thyrotropic Hormone of the Pituitary Gland, J. Biol. Chem. **109**: lxii-lxiii (May) 1935. Cuyler and others.[22] Stimmel and others.[26]

49. (*a*) Collip, J. B.: The Standardization of Anterior Pituitary Hormones, Am. J. Obst. & Gynec. **33**: 1010-1016 (June) 1937. (*b*) Hertz, Saul, and Oastler, E. G.: Assay of Blood and Urine for Thyreotropic Hormone in Thyrotoxicosis and Myxedema, Endocrinology **20**: 520-525 (July) 1936.

olism of the rat is restored to normal by the thyrotropic factor, a change which has been advocated for bioassay purposes.[50] However, in view of the more recent discoveries showing that pituitary extracts other than those containing the thyrotropic principle may raise the basal metabolic rate, this method is not strictly specific.

Among other assay methods in which the rat is used should be mentioned that of Cuyler and co-workers,[22] which is based on the action of the thyrotropic hormone in decreasing the iodine of the thyroid, and that of Karnofsky and Cronkite,[51] based on the observation that this principle accelerates the eruption of the incisor teeth in the newborn rat.

Thyrotropic Content of Blood.—Van Caulaert and associates [52] found that dog serum has the ability to stimulate the thyroid of the immature guinea pig. Fellinger [53] prepared an extract of dog blood which was definitely thyrotropic in the guinea pig. Horse serum likewise shows thyrotropic activity.[52]

Guinea pig blood, unlike that of most other species so far examined, does not contain any thyrotropic principle demonstrable by the guinea pig thyroid test.[54]

Rabbit and rat blood are definitely thyrotropic in the guinea pig thyroid test.[52] Aron [55] claimed that rat blood is particularly active in stimulating the thyroid of the immature rabbit.

Human blood is active in producing thyroid hyperplasia in immature guinea pigs.[56] Fellinger [53] showed that the active substance is readily extracted from the serum by 40 per cent acetone, from which it precipitates after the concentration is raised to 85 per cent. Aron [55] claimed that the thyrotropic activity may also be demonstrated by the effect of normal human blood on the thyroid of the immature rabbit.

Thyrotropic Content of Urine.—Emerson and Cutting [57] were unable to demonstrate any thyrotropic substance in dog urine using the guinea pig thyroid test. Similar negative results have been obtained with guinea pig urine by Aron,[54] who used the same test. Rat urine, on the other hand, is very active in stimulating the thyroid of the immature guinea pig.[58]

Aron and collaborators [59] and Starr and associates [45] were able to demonstrate in the urine of man the presence of thyrotropic substance, using the thyroid of either the guinea pig or the rabbit as an indicator. Katzman and Doisy [60] stated that a modification of their tungstic acid process for the extraction of the gonadotropic factor from pregnancy urine is suitable for the extraction of a thyrotropic substance from urine. Nielsen [61] claimed that the urine of some men stimulates, while that of others depresses, thyroid development in the rabbit. Antognetti and Geriola [62] and Emerson and Cutting [57] found normal urine quite inactive in the guinea pig thyroid test. Similarly, Jones [63] was unable to extract the thyrotropic principle from normal urine with a method which gave good recoveries when a pituitary extract containing this principle was simply added to urine. He concluded that either the hormone is not excreted in an active form or its chemical properties are so altered that it is not extractable with his method. Giedosz,[64] on the other hand, observed marked stimulation of the rabbit thyroid following administration of normal human urine. Sendrail and Tamalet [65] claimed that 15 cc. of normal urine (the amount employed for one 3 day assay) contains from 4 to 30 Aron guinea pig units.

Thyrotropic Content of Blood and Urine in Various Diseases.—In Simmonds's disease the thyrotropic activity of the urine is below normal as judged by the guinea pig thyroid test.[66]

In acromegaly Fellinger [53] was able to recover thyrotropic substance in unusually large quantities from the blood, using his acetone extraction method. The urinary excretion of thyrotropic substance is increased in this disease, according to Nitzescu and Timus [67] and Sendrail and Tamalet,[65] who used the guinea pig thyroid test. The latter investigators obtained similar results in Cushing's disease. On the other hand, Jones,[63] who used the chick for assay, obtained negative results.

In myxedema and other types of hypothyroidism Aron,[68] Aron and Klein [32] and Antognetti and Geriola [62] obtained variable results, while Hertz and Oastler,[49b] who followed restoration of the thyroid in hypophysectomized rats, and Rawson and Starr [44] and Sendrail and Tamalet,[65] who employed the guinea pig thyroid test, observed increased elimination of thyrotropic substance. Emerson and Cutting,[57] using the latter test, found that following thyroidectomy the thyrotropic activity of the blood increases regularly, but such increase is only occasionally observed in spontaneous hypothyroidism. Jones,[63] who with his chick test could not detect any thyrotropic substance in the urine of normal persons or patients suffering from a variety of diseases, found a positive result in a case of myxedema.

The blood of patients with hypothyroidism is rich in thyrotropic substance, according to Fellinger,[53] Hertz and Oastler [49b] and Bodart and Fellinger,[56b] who also noted that following thyroidectomy the usually low thyrotropic activity of the blood of patients suffering from exophthalmic goiter undergoes a rapid and pronounced increase. It appears that the production of thyrotropic hormone is increased in thyroid insufficiency just as the output of gonadotropic hormone rises after the gonads are removed or have undergone involution.

In hyperthyroidism Aron [68a] obtained variable results, while Krogh and Okkels [69] claimed that no thyrotropic activity can be demonstrated in the urine by the rabbit

50. Anderson, E. M., and Collip, J. B.: Studies on the Physiology of the Thyreotropic Hormone of the Anterior Pituitary, J. Physiol. **82:** 11-25 (Jan.) 1934.

51. Karnofsky, D., and Cronkite, E. P.: Effect of Thyroxine on Eruption of Teeth in Newborn Rats, Proc. Soc. Exper. Biol. & Med. **40:** 568-570 (April) 1939.

52. van Caulaert, C.; Aron, Max, and Stahl, J.: Sur la présence de l'hormone préhypophysaire excito-sécrétrice de la thyroïde dans le sang et le liquide céphalo-rachidien, et sur sa repartition dans ces milieux et dans l'urine, Compt. rend. Soc. de biol. **106:** 607-609 (Feb. 13) 1931.

53. Fellinger, Karl: Klinische und experimentelle Untersuchungen über das Verhalten und die Bedeutung des thyreotropen Hormons im Blute, Wien. Arch. f. inn. Med. **29:** 375-406, 1936.

54. Aron, Max: Recherches sur les indices d'activité de la préhypophyse selon l'âge et l'espèce par la méthode du titrage physiologique de l'hormone dans le milieu intérieur, et sur leur correspondance avec les manifestations morphologiques de l'activité de la thyroïde, Comp. rend. Soc. de biol. **106:** 609-611 (Feb. 27) 1931. van Caulaert and others.[52]

55. Aron, Max: Distinction entre l'hormone préhypophysaire excito-sécrétrice de la thyroïde et le principe stimulant de l'ovaire renfermé dans les extraits préhypophysaires, Compt. rend. Soc. de biol. **106:** 1044-1046 (April 16) 1931.

56. (*a*) Aron, Max; van Caulaert, C., and Stahl, J.: Recherches sur le diagnostic des troubles fonctionnels du lobe antérieur de l'hypophyse (préhypophyse) et sur certains déséquilibres endocriniens auxquels ils participent, Presse méd. **40:** 1981-1984 (Dec. 31) 1932. (*b*) Bodart, F., and Fellinger K.: Ueber die thyreotrope Wirkung des Serums bei endokrinen Erkrankungen, Wien. klin. Wchnschr. **49:** 1286-1287 (Oct.) 16) 1936. (*c*) Aron.[31d] (*d*) Caulaert and others.[52]

57. Emerson, Kendall, Jr., and Cutting, W. C.: Urinary Thyrotropic Hormone, Endocrinology **23:** 439-445 (Oct.) 1938.

58. Aron, Max; van Caulaert, C., and Stahl, J.: L'équilibre entre l'hormone préhypophysaire et l'hormone thyroïdienne dans le milieu intérieur à l'état normal et à l'état pathologique, Compt. rend. Soc. de biol. **107:** 64-66 (May 8) 1931.

59. Aron, Max: L'hormone thyréo-stimulante de la préhypophyse est-elle éliminée par le rein et présente dans l'urine? Compt. rend. Soc. de biol. **114:** 20-23, 1933; L'hormone thyreo-stimulante de la préhypophyse est-elle présente dans l'urine? ibid. **116:** 272-273, 1934. Aron.[31d] Aron.[55] Aron and others.[56] Aron and Klein.[32]

60. Katzman, P. A., and Doisy, E. A.: A Quantitative Procedure for Determining Normal Excretion of Prolan, Proc. Soc. Exper. Biol. & Med. **30:** 1188-1191 (June) 1933.

61. Nielsen, Herman: Ein "Thyreotest" durch Harninjektion in Kaninchen, Klin. Wchnschr. **12:** 508 (April 1) 1933.

62. Antognetti, L., and Geriola, F.: Studi sui "tests" ormonici: Nota tredicesima. L'hormone tireotropo preipofisario, Endocrinol. e. pat. costit. **11:** 395-410 (July) 1936.

63. Jones, M. S.: A Study of Thyrotropic Hormone in Clinical States, Endocrinology **24:** 665-671 (May) 1939.

64. Giedosz, B.: Ueber thyreotrope Substanzen im menschlichen Harn, Klin. Wchnschr. **13:** 1507 (Oct. 20) 1934.

65. Sendrail, M., and Tamalet, L. J.: Le test hypophysaire d'Aron en clinique, Toulouse-méd. **40:** 1-15 (Jan.) 1939.

66. Anderson and Collip.[50] Sendrail and Tamalet.[65]

67. Nitzescu, I. I., and Timus, D.: Die Ausscheidung des thyreotropen Hormons aus dem Hypophysenvorderlappen durch den Harn bei Akromegalie, Spitalul **58:** 5, 1938.

68. Aron, Max: (*a*) Méthode biologique de diagnostic des états d'hyperactivité et d'hypoactivité de la préhypophyse chez l'homme, Compt. rend. Soc. de biol. **105:** 585-586 (Nov. 28) 1930; (*b*) Le titrage des hormones préhypophysaires dans l'urine humaine; son intérêt dans l'exploration fonctionelle des diverses glandes endocrines, Bull. Acad. de méd. **111:** 273-275 (Feb. 20) 1934.

69. Krogh, Marie, and Okkels, Harald: L'hormone thyréostimulante préhypophysaire est-elle présente dans l'urine? Compt. rend. Soc. de biol. **113:** 635-638, 1933; L'hormone thyréostimulante préhypophysaire est-elle eliminée par le rein? ibid. **113:** 638-641, 1933.

thyroid test. Smith and Moore,[70] Antognetti and Geriola,[62] Emerson and Cutting,[57] Rawson and Starr,[44] Starr and other co-workers [45] and Sendrail and Tamalet,[65] all of whom used the guinea pig thyroid test, usually found subnormal quantities of thyrotropic substance in the urine, and in most cases this principle appeared to be entirely absent. Jones,[63] who used the chick test, likewise failed to detect excretion of thyrotropic substance. Drouet [71] emphasized, however, that increased excretion of thyroxine, which may antagonize the effect of the thyrotropic hormone in the intact animal, may be the reason why most investigators were unable to detect the latter factor in the urine of hyperthyroid patients. He pointed out that negative results from urinary assays do not prove that thyrotropic substance is not excreted unless it is made certain that no substances antagonistic to the thyrotropic hormone are eliminated. It should be emphasized, however, that Hertz and Oastler,[40b] who used hypophysectomized rats for their assays, were also unable to demonstrate thyrotropic activity in the urine of hyperthyroid patients, although in the absence of the pituitary the thyroid hormone would not have exerted an inhibitory effect. It is of interest, however, that, according to Nielsen,[61] in exophthalmic goiter the urine actually causes atrophy of the epithelium in the rabbit thyroid, which suggests some antithyrotropic effect.

The blood of patients with hyperthyroidism likewise contains subnormal amounts of thyrotropic substance, according to the guinea pig assays of Fellinger [53] and Bodart and Fellinger.[56b]

In obesity Merklen and co-workers [72] invariably observed an increase in the elimination of thyrotropic substance, using the guinea pig test, while de Prat [73] obtained more variable results.

In various other diseases the results so far reported are too contradictory to justify detailed comment.[74] It is noteworthy, however, that, according to Aron,[74a] in most cases the elimination curves of the thyrotropic and gonadotropic substances tend to run parallel.

Preparation of Active Extracts.—Greep [75] showed that a fairly complete separation of thyrotropic from gonadotropic substance could be obtained by treatment of extracts with benzoic acid. The thyrotropic factor was precipitated with the benzoic acid, and the gonadotropic factor remained in the filtrate.

Lambie and Trikojus [76] have recently described a method of extraction and purification of the thyrotropic principle. Collip [77] has found that, in addition to the thyrotropic substance which is obtained in primary dilute acetic acid extracts, an isoelectric protein fraction can be prepared from the gland residues which is highly potent in thyrotropic properties. Moreover, guinea pigs treated daily with the latter fraction may not show resistance to it for many months. This is confirmatory of the results of Werner,[78] who found that thyrotropic extracts prepared by different methods differed widely in their ability to cause development of the refractory state in guinea pigs.

Effect of Iodine on Action of Thyrotropic Hormone.—Friedgood [79] has reported that the administration of sodium iodide to guinea pigs receiving an extract containing the thyrotropic factor caused a remission of the symptoms of hyperthyroidism. Anderson and Evans [80] observed that in guinea pigs potassium iodide may prevent the metabolic action of thyrotropic extracts (perhaps because it prevents the discharge of thyroxine) without interfering with the effect on the thyroid itself. Franck [81] found in guinea pigs treated with an extract of the anterior lobe that the basal metabolism decreased after an initial increase. During the period of decreased basal metabolic rate the thyroid showed storage of colloid. This storage appeared simultaneously with an enlargement of the Golgi apparatus and was considered to be due to a special action of the thyrotropic principle. Iodine administered to such animals prevented both the initial rise and the eventual fall in the basal metabolic rate. According to Franck, extracts of the anterior lobe cause degranulation of the eosinophils and an increase in the number of basophils in the anterior lobe of the guinea pig. These effects are inhibited by iodine. He concluded that the basophils of the pituitary secrete a thyrotropic hormone which stimulates storage of colloid in the thyroid follicles. The secretion of this hormone is prevented by the administration of iodine.

THE PARATHYROTROPIC HORMONE

Although the existence of a parathyrotropic hormone has not been proved as yet and may be regarded as rather doubtful, certain clinical and experimental evidence now available concerning this question will be discussed.

Parathyroid Tumors.—Adenoma of the parathyroids has repeatedly been observed in association with hypophysial tumors,[82] a fact which suggests that a close relationship exists between these two glands.

Hypophysectomy.—In the dog Aschner [83] was unable to detect any change in the parathyroids following ablation of the hypophysis, while Koster [84] claimed that the parathyroids were invariably subnormal in size. Houssay and Sammartino [85] stated that degenerative lesions

70. Smith, M. G., and Moore, E.: Is Anterior Pituitary Hormone Demonstrable in Urine of Graves' Disease, in Urine of Guinea Pigs Injected with Anterior Pituitary Extract, Proc. Soc. Exper. Biol. & Med. **30:** 735-739 (March) 1933.

71. Drouet, P. L.: Le rôle de l'hypophyse dans l'hyperthyroïdie et le syndrome para-basedowien. Contribution à l'étude de l'hyperpituitarisme, Rev. franç. d'endocrinol. **12:** 101-136 (April) 1934.

72. Merklen, P.; Aron, Max; Israel, L., and Jacob, A.: Tests histologiques de l'hyperfonctionnement préhypophysaire chez certains obèses, Bull. et mém. Soc. méd. d. hôp. de Paris **51:** 1402-1406 (Nov. 4) 1935.

73. de Prat, J.: Thesis, Paris, 1937.

74. (*a*) Aron, Max: Parallélisme des taux respectifs d'excrétion de la thyréo-stimuline et de la gonado-stimuline préhypophysaires dans le milieu intérieur chez l'homme en des conditions normales ou pathologiques, Compt. rend. Soc. de biol. **113:** 443-445, 1933. (*b*) Sendrail and Tamalet.[65]

75. Greep, R. O.: Separation of a Thyrotropic from the Gonadotropic Substances of the Pituitary, Am. J. Physiol. **110:** 692-699 (Jan.) 1935.

76. Lambie, C. G., and Trikojus, V. M.: The Preparation of a Purified Thyrotropic Hormone by Chemical Precipitation, Biochem. J. **31:** 843-847 (June) 1937.

77. Collip, J. B.: Anterior Pituitary Hormones, in Piersol, G. M., and Bortz, E. L.: Cyclopedia of Medicine, Surgery and Specialties, Philadelphia, F. A. Davis Company, 1939, pp. 637-656.

78. Werner, S. C.: Prolonged Injection of a Thyrotropic Extract Without Development of Refractoriness, Proc. Soc. Exper. Biol. & Med. **34:** 390 (April) 1936; Antibody Nature of Refractoriness to Injections of Hypophyseal Extracts Containing Thyrotropic Hormone, ibid. **34:** 392 (April) 1936.

79. Friedgood, H. B.: Similarity of the Iodin Remission in Experimental Anterior Hypophyseal Hyperthyroidism, the Hyperthyroidism of Acromegaly and That of Exophthalmic Goiter, Endocrinology **20:** 526-536 (July) 1936.

80. Anderson, E. M., and Evans, H. M.: The Effect of Thyreotropic Hormone Combined with Small Amounts of Iodine upon the Function of the Thyroid Gland, Am. J. Physiol. **120:** 597-603 (Nov.) 1937.

81. Franck, S.: Histophysiologie de la préhypophyse. Prehypophyse et glande thyroïde soumises à l'action de l'iode, Compt. rend. Soc. de biol. **125:** 569-573 (Feb. 26) 1937.

82. Hadfield, G., and Rogers, H.: Two Parathyroid Tumors Without Osteitis Fibrosa: One Associated with Acromegaly, J. Path. & Bact. **35:** 259-263 (March) 1932. Gerstel, G.: Ueber multiple Tumoren der Drüsen mit innerer Sekretion bei einem Akromegalen, Frankfurt. Ztschr. f. Path. **52:** 485-499, 1938. Husslein, J.: Zur Frage der Pagetschen und Recklinghausenschen Knochenerkrankung, Beitr. z. klin. Chir. **169:** 276-298, 1939.

83. Aschner, B.: Ueber die Funktion der Hypophyse, Arch. f. d. ges. Physiol. **146:** 1-146, 1912.

84. Koster, S.: Étude expérimentale de la fonction de l'hypophyse chez le chien, Arch. néerl. de physiol. **13:** 601, 1928; Experimentelle Untersuchungen der Hypophysenfunktion der Hunde: II. Arch. f. d. ges. Physiol. **224:** 212-216, 1930.

85. Houssay, B. A., and Sammartino, R.: Les parathyroïdes dans l'insuffisance hypophysaire et pancréatique, Compt. rend. Soc. de biol. **114:** 729-732, 1933; Die Epithelkörperchen bei den Hypophysen- und Pankreasinsuffizienzen des Hundes, Beitr. z. path. Anat. u. z. allg. Path. **93:** 405-416 (July) 1934.

and necrosis of the parathyroids may be observed in 66 per cent of all hypophysectomized dogs, while they are seen in only 10 per cent of the normal controls. After lesions of the tuber cinereum they were noted in about 41 per cent of the cases.

In the rat Smith [86] claimed to have noted atrophy of the parathyroids following hypophysectomy.

Hypophysectomy and Pancreatectomy.—The degenerative changes which occasionally occur following hypophysectomy are much more commonly observed in the dog in which the pancreas is also removed. Mere removal of the pancreas, however, does not elicit such changes except in rare cases.[87]

Hypophysial Extracts.—In the cat Anselmino and co-workers [88] claimed that the so-called parathyrotropic extracts of the pituitary cause hyperemia and histologic signs of increased activity in the parathyroids without actually increasing their size.

In the dog, following treatment with hypophyseal extract, enlargement of the epithelial cells, follicle formation and hyperemia have been observed without enlargement of the total volume of the gland,[88] and the structural changes were often accompanied by hypercalcemia.[89] Recently Ham [90] reported changes supposedly characteristic of the parathyrotropic hormone in the parathyroids of dogs treated with pituitary extract.

In the guinea pig Anselmino and associates [88] also claimed to have seen parathyroid stimulation after the administration of pituitary extract.

In the dwarf mouse Kemp and Marx [91] claimed to have seen parathyroid enlargement following administration of a preparation containing the growth-promoting factor of the anterior lobe.

In the rabbit Hertz and Kranes,[92] Anselmino and associates [88] and Cattaneo [93] observed enlargement and changes after treatment with various pituitary extracts, which they interpreted as characteristic of the parathyrotropic hormone.

In the rat Anselmino and co-workers [94] claimed to have obtained particularly obvious parathyroid enlargement accompanied by hypercalcemia following treatment with their extract of the parathyrotropic factor, and Hoffmann and Anselmino [89] emphasized that the hypercalcemia is prevented by parathyroidectomy.

It should be emphasized, however, that the existence of the parathyrotropic hormone has by no means been proved.[95]

86. Smith, P. E.: The Disabilities Caused by Hypophysectomy and Their Repair, J. A. M. A. **88**: 158-161 (Jan. 15) 1927.

87. Houssay, B. A., and Biasotti, A.: La diabetes pancreática de los perros hipofisoprivos, Rev. Soc. argent. de biol. **6**: 251-296, 1930. Houssay, B. A., and Sammartino, R.: Altérations des parathyroïdes des chiens pancréatoprivés, Compt. rend. Soc. de biol. **120**: 735-736, 1935. Houssay and Sammartino.[85] Collip.[6]

88. Anselmino, K. J.; Herold, L., and Hoffmann, F.: Ueber die Wirkung des parathyreotropen Hormons des Hypophysenvorderlappens bei verschiedenen Tierarten, Ztschr. f. exper. Med. **97**: 51-59, 1935.

89. Hoffmann, F., and Anselmino, K. J.: Ueber die Wirkung von Hypophysenvorderlappenextrakten auf den Blutkalkspiegel, Klin. Wchnschr. **13**: 44-45 (Jan. 13) 1934.

90. Ham, A. W., and Haist, R. E.: Histological Effects of Diabetogenic Anterior Pituitary Extracts, Anat. Rec. **76** (supp. 2): 89 (Feb.) 1940.

91. Kemp, Tage, and Marx, Lore: Beeinflussung von erblichem hypophysärem Zwergwuchs bei Mäusen durch verschiedenen Hypophysenauszüge und Thyroxin: II. Endokrine Organe, Acta path. et microbiol. Scandinav. **14**: 197-227, 1937.

92. Hertz, Saul, and Kranes, Alfred: Parathyreotropic Action of the Anterior Pituitary: Histologic Evidence in the Rabbit, Endocrinology **18**: 350-360 (May-June) 1934.

93. Cattaneo, M.: Richerche sperimentali sull'ormone paratireotropo del lobo anteriore dell'ipofisi, Riv. di pat. sper. **9**: 361-370, 1938.

94. Anselmino, K. J.; Hoffmann, F., and Herold, L.: Ueber die parathyreotrope Wirkung von Hypophysenvorderlappenextrakten, Klin. Wchnschr. **13**: 1944 (Dec. 16) 1933.

95. Bomskov, Christian: Methodik der Hormonforschung., Leipzig, Georg Thieme, 1939, vol. 2.

Special Clinical Article

CHEMOTHERAPY IN UROLOGY

CLINICAL LECTURE AT NEW YORK SESSION

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As in all fields of medicine, the advent of sulfanilamide and its derivatives has been a welcome addition to the armamentarium of the urologist. Almost a decade ago chemotherapy in urology made its first real step forward with the use of the ketogenic diet in the treatment of infection of the urinary tract. This rather cumbersome therapeutic agent was shortly followed by the discovery that mandelic acid is of equal value and much easier to administer. These therapeutic measures depended for their effectiveness on a certain concentration of an organic acid in the urine at a p_H level below 5.5. Even when the desired conditions were met, many infections did not respond to such therapy. It was evident that, when a gram-negative bacillus or Streptococcus faecalis was present, bacteriostasis was the rule and the organism could be eradicated. However, when Staphylococcus aureus or albus, Micrococcus or the hemolytic or green-producing streptococcus was present these agents were not effective in destroying the organisms. The need for an adjunct to the treatment of such urologic conditions was apparent and the early reports concerning the use of sulfanilamide and its derivatives have stimulated investigation in the field of infections of the urinary tract.

The effectiveness of the sulfonamide compounds in the treatment of bacterial infections has entirely changed the practice of therapy within a few years. Owing to the chemical reactivity of the parent substance, countless derivatives have been synthesized and their therapeutic action has been determined. It is not within the scope of this paper to go into the history of the development of these compounds. Neither is it possible to discuss the entire gamut of those derivatives of sulfanilamide which have been used in the treatment of urologic diseases associated with or caused by bacterial invasion.

Before the actual use of these compounds in urology is discussed, a word or two concerning the mode of action seems indicated. Undoubtedly a direct action on the organism does take place both in vitro and in vivo. In urology the actual presence of the drug in the urine in the free form undoubtedly is a factor in its effectiveness, and its presence in tissue fluids enables it to reach the deeper seated infections. Whether or not the sulfonamide compounds have any effect on the immune processes of the body has been a point of controversy. The body defenses are important and necessary factors in the final curative effects, but whether phagocytosis is truly stimulated by the administration of these drugs is not definitely known at this time. More recently the bacteria-destroying property of the drug has been attributed to the accumulation of hydrogen peroxide due to the inactivation of catalase by the drug.

Turning now to the discussion of the clinical aspects of the use of the sulfonamide compounds, the main factors influencing the results obtained are the type of

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organism present, the type of case being treated, the mode of administration and dosage used, and the patient's ability to tolerate the drug as evidenced by signs of toxicity.

TYPE OF ORGANISM

Early in our work from experimental and clinical data my associates and I became aware of the fact that sulfanilamide and its more closely related derivatives, such as disulfanilamide, dimethyldisulfanilamide and sulfanilyl-sulfanilamide, were most effective against the gram-negative bacilli and the beta-hemolytic streptococcus. The same was true for azosulfamide. The organisms of the genus Proteus have always presented a most difficult problem. Because of their urea-splitting property, chemotherapy requiring acidification of the urine was usually of little value because of the difficulty in producing the desired acidity. The sulfonamide compounds have been most useful in treating infection produced by this organism because these drugs in most instances are more effective in an alkaline medium. Staphylococcus, micrococcus and Streptococcus faecalis were usually not affected by these drugs with the exception of dimethyldisulfanilamide, which has never been marketed in this country because of the too frequent complication of peripheral neuritis largely involving the motor nerves. The gonococcus was attacked with considerable ease in the properly managed infection, but in many instances "sulfanilamide-resistant" cases were reported and the need for an additional chemotherapeutic agent became apparent.

The early experimental work with sulfapyridine showed little advantage in the treatment of infections of the urinary tract caused by the gram-negative bacilli or the streptococci. However, it was of some value in the group caused by the staphylococci. Because of the early reports concerning its action on the pneumococcus we used it in the treatment of infection produced by a similar organism, the gonococcus. Its efficacy here was much greater than that of sulfanilamide.

More recently we have had the opportunity to use another derivative, sulfathiazole, in the treatment of infections of the urinary tract. Again the usual gram-negative bacilli are destroyed by its administration. Of great interest to all of us is the fact that this drug is effective in eradicating staphylococcus and micrococcus, which were so resistant to the other sulfonamide compounds. The beta hemolytic streptococcus does not respond as well and in only about 30 to 40 per cent of the early cases was Streptococcus faecalis destroyed. Recently Helmholz has shown experimentally that the level of the p_H of the urine in vitro has a marked effect on the bactericidal property of sulfathiazole against Streptococcus faecalis. At a p_H of 5.0 a concentration of from 25 to 50 mg. per hundred cubic centimeters destroys the organism. As the degree of acidity decreases, a greater concentration of the drug becomes necessary until, at a p_H of 7.5, 200 mg. per hundred cubic centimeters will do little more than produce some bacteriostasis. We have been able to confirm this clinically.

Sulfathiazole, however, is the drug *par excellence* in the treatment of gonorrhea. To date we have treated only a group of sixteen patients suffering with this disease, but in all of them the gonococcus has been effectively destroyed within one week of the start of the administration of sulfathiazole. In the usual case the discharge disappears within three or four days and the two glass test shows both glasses of urine to be clear macroscopically and microscopically. At this time the prostate is massaged and, if the secretion shows evidence of infection, regular prostatic treatment is instituted consisting of massage, irrigations and instillations as needed. If the prostatic secretion is negative, it is rechecked in another two or three days and if it still does not show any evidence of infection no further examination or therapy to the prostate is indicated.

TYPE OF CASE

Knowing the exact pathologic condition present in each case of infection of the urinary tract is just as important as knowing the exact organism responsible for the infection. By no means do I wish to imply that each patient who presents himself with the complaint of burning and frequent urination should be submitted to an extensive urologic investigation. Beyond any doubt, from the history and the initial examination our clinical judgment will decide its need in most instances. However, if after one or two satisfactory courses of chemotherapy the desired improvement and cure have not been gained or if repeated reinfection occurs, we must make certain that we are not dealing with complicating pathologic conditions such as stone, tumor, obstruction, foreign body or deep seated infection producing cicatrization and scarring of some part of the urinary tract.

Experience has taught us that in the simple uncomplicated cases of infection of the urinary tract almost any of the sulfonamide compounds is effective in destroying the disease in more than 90 per cent of the cases. Interestingly enough, this holds for the cases in which the infection is in the kidney as well as in those cases in which it is confined to the bladder alone, provided there is no cicatricial deformity or complications previously described. Early in our efforts we noted the inhibiting effect of chronic prostatitis on the efficacy of urinary antiseptics. The percentage of cases in which cures are effected is reduced almost a half unless the prostatic infection is adequately treated at the time of the drug therapy. It is not the rule that any of the sulfonamide compounds is regularly useful in treating nonspecific prostatitis. In certain cases in which the infecting organism in the urine can also be recovered from the prostatic secretion, good results may follow sulfanilamide therapy. Little more need be said concerning the usual complicating pathologic conditions found and the treatment required in certain infections of the urinary tract. Stone, foreign bodies and tumors should be removed; obstruction should be relieved. Unless this is done, only rarely shall we find the sulfonamide compounds of any use in the treatment of associated infection.

When the infection in the kidneys is of long standing and considerable cicatricial deformity, and perhaps caliectasis, have been produced, the problem of therapy is considerably more difficult. As mentioned previously, the action of the drug depends on its presence and concentration in the body fluids as well as in the urine. However, many observers believe the latter fact is the most important and consequently to obtain a bacteriostatic or bactericidal action in the urine we must have a kidney functioning well enough to excrete the drug. An infected, poorly functioning kidney will be benefited only to the extent to which the drug can be excreted by it. A most interesting observation has been that the sulfonamide compounds, and particularly azosulfamide, may be administered in moderate dosage to such patients with little chance of injuring these poorly functioning kidneys. This is not true when using

mandelic acid or the ketogenic diet, as with the latter therapeutic agents function is usually more impaired and the treatment must be stopped. More recently we have been using some of the newer sulfonamide compounds, particularly sulfathiazole, and, much to our surprise, have found the last mentioned drug to be more effective in the chronic case of pyelonephritis in which the kidneys show the typical chronic inflammatory changes such as cicatricial deformity and caliectasis with slight to moderate reduction in function as evidenced by the excretory urogram.

MODE OF ADMINISTRATION AND DOSAGE

The sulfonamide compounds when given to man may be given orally or parenterally. These drugs are almost entirely eliminated in the urine, partly in a free state and partly in a conjugated form, as an acetylated compound. It is the free form which exerts the bacteriostatic and bactericidal effect. When given orally the rate of absorption of these drugs varies with different cases and with the drug used, but usually two or three days is required to establish equilibrium between the amount ingested and the amount excreted. Somewhat less time seems to be necessary when sulfapyridine or sulfathiazole is administered. In certain instances oral ingestion is impossible for various reasons, and in these cases parenteral injection has been of great value. Sulfanilamide powder may be prepared in an 0.8 per cent solution in physiologic solution of sodium chloride and given subcutaneously. In this way a patient may be given more than 100 grains (6.5 Gm.) of the drug daily with little difficulty. The sodium salt of sulfapyridine may be given intravenously and some observers have recently shown that sulfathiazole may be given in the same way. The intravenous use of these drugs is useful in building up rapidly an appreciable level of the drug in the blood, particularly for those patients who have difficulty in taking the drug by mouth. The disadvantage, however, is that while the concentration in the blood is built up rapidly it also decreases rapidly and frequent administrations are necessary if an adequate concentration is to be maintained.

Clinically I do not feel that determinations of the level of these compounds in the blood are necessary in the satisfactory handling of patients suffering with infections of the urinary tract. Many estimations have been made and only in rare instances have I seen concentrations more than from 5 to 6 mg. per hundred cubic centimeters with the dosage usually used. I believe that a greater concentration in the blood is rarely needed to destroy an existing infection.

In the field of infection of the urinary tract the oral and subcutaneous administrations are usually sufficient. Various dosage levels have been suggested by many observers. However, it has been my experience that in the majority of instances sulfanilamide and its more closely related derivatives need seldom be given in a dosage greater than 40 grains (2.6 Gm.) daily. This is given in equal doses four times a day. The ease of administration may be enhanced by supplementing each dose with a similar quantity of sodium bicarbonate. The addition of the latter drug may have an additional value in that Helmholz and Sickler have shown that the efficacy of sulfanilamide in the urine is increased at a p_H level of 7.5. If sulfanilamide must be given parenterally, a somewhat greater dosage is advised, as previously mentioned.

Azosulfamide, while not as effective as sulfanilamide in equal doses, is of great value in urologic work. It is given in a dosage of 60 grains (4 Gm.) daily and may have to be used over a somewhat longer period. Usually sulfanilamide or azosulfamide is given for a period of from eight to fourteen days. At the end of that time we have deemed it advisable to stop the drug whether the urine has been sterilized or not. An intervening period of two or three weeks followed by a second course of the medication will frequently bring about the desired results. In a number of cases we have found a second and third course of the drug necessary before sterilization takes place.

Sulfapyridine has not been used extensively in this country in the treatment of the usual bacillurias and cocciurias. Foreign observers report little advantage for it over sulfanilamide in such cases. However, in the treatment of gonorrhea it has been of great value. We have regularly used a dosage of 45 grains (3 Gm.) daily for a period of from ten to fourteen days. If the urine in such cases is not grossly clear and the urethral discharge is not stopped within three days the dosage is increased to 60 grains (4 Gm.) daily. The drug is best given with milk and this will relieve much of the nausea attending its use.

More recently another derivative of sulfanilamide, namely sulfathiazole, has been added to our armamentarium. The original dosage used was 60 grains (4 Gm.) daily but recent work has led me to believe that in most cases 45 grains (3 Gm.) will be sufficient. This is given in divided doses by mouth and if it is at all nauseating its administration is likewise eased by giving it with milk. As previously mentioned, it has proved to be of inestimable value in the therapy of staphylococcic and gonococcic infections. In the latter conditions I believe that 60 grains (4 Gm.) daily is advisable and I have continued this for a period of from ten to fourteen days, although in all our cases the discharge was stopped and the urine was clear in from three to four days. Local treatment is instituted as previously described under the discussion concerning sulfapyridine.

TOXIC MANIFESTATIONS

When one surveys the many contributions to the literature with regard to the untoward reactions noticed following the administration of the sulfonamide compounds, the need for careful observation of each patient taking the drug becomes apparent. It is true that in the management of infections of the urinary tract these untoward reactions are less frequent than in the general field of therapy. Signs of toxicity may be due to sensitivity or idiosyncrasy to the medication. While the latter is more severe, it is less common. Sensitivity to the drug is more frequently noted to a greater or lesser degree and is almost always related to the dosage used and the total amount administered.

I have made it a practice never to administer any of the sulfonamide compounds unless the patient can be seen in from twenty-four to forty-eight hours. With this scheme I feel that we have been able to avert some of the more serious reactions frequently experienced. No doubt the main reason for the relative infrequency of the more serious toxic manifestations is the reduced dosage which has been found satisfactory in our field. Headache, malaise, vertigo, tinnitus, anorexia and nausea are frequently seen to a mild degree and usually will disappear on the third or fourth day the drug is taken. Patients with these mild to moderate symptoms should be observed closely, as these symptoms may be the precursors of more serious reactions. Cyanosis of a mild degree may be disregarded, but if it increases I

believe this is enough to warrant stopping the drug, as it may be an indication of an impending blood dyscrasia. It has been stated that sulfanilamide injures the blood-forming organs in from 4 to 5 per cent of cases. Hemolytic anemia of the acute and chronic form has been frequently reported, the acute form coming on within the first week of therapy and the chronic form not being seen for two or three weeks after treatment has begun. The development of granulocytopenia usually comes after the administration of large doses or prolonged treatment. It is a severe reaction and usually fatal. Unquestionably many of these blood conditions following administration of sulfanilamide could be avoided with more careful and frequent observation of patients. I am certain that a few extra blood counts when cyanosis is developing would often aid in averting these serious complications.

Dermatitis is a rather frequent complication and is of two types, the one localized to the exposed parts and the other a more general eruption over the entire surface of the body. The former type is caused by an increased sensitivity of the skin to light as a result of ingestion of the drug. The latter type is a toxic dermatitis. The presence of either form requires stopping the drug, but it can be resumed at a later date in the former type if the patient is instructed to keep out of the sunlight while taking the drug. With all the sulfonamide compounds I have found the dermatitis to be more likely to occur during the second course of the administration of these drugs, particularly if the second course of the drug is begun within eight days of the previous course. A certain sensitization must occur and the same fact has been noted by other observers. By prolonging the period between courses I feel that the frequency with which dermatitis occurs has been definitely reduced.

Sulfapyridine produces in general the same toxic disturbances as sulfanilamide but these are less severe with few exceptions. Nausea is more common but can frequently be relieved by taking the drug with milk. Gastric disturbances following the ingestion of sulfapyridine present but a small problem to the urologist as compared to the general physician because the former rarely needs to use large doses. A very important toxic sign is evidence of irritation along the urinary tract. As with sulfanilamide, an acetylated derivative of sulfapyridine is formed within the body and excreted in the urine. Crystals of this substance are frequently found in the urine of patients taking the drug and no doubt produce hematuria, either gross or microscopic, in approximately 5 per cent of cases. This complication is not important usually, but cases have been reported in which necropsy has shown complete casts of the calices, pelves and ureters when large doses of the drug have been taken.

Azosulfamide and sulfanilyl-sulfanilamide produce similar toxic reactions to sulfanilamide itself but as a rule these side-effects are of a milder degree. Dimethyldisulfanilamide and more recently sulfamethylthiazole, two drugs of generally lessened toxicity, have had to be discarded because of the frequency with which peripheral neuritis has appeared after their use. The same complication has occurred after sulfanilyl-sulfanilamide, only much less frequently.

For some months I have been using sulfathiazole and find it much less toxic than the parent substance. The usual symptoms seen after ingestion of sulfanilamide appear here also, but they are less severe. As yet I know of no disturbances simulating the nerve lesion previously mentioned as following the administration of sulfamethylthiazole. Dermatitis does occur but again I have been able to decrease the incidence of this complication by prolonging the first course of the drug and waiting at least two weeks before again giving it in any dosage.

SUMMARY

Sulfanilamide and its related compounds have proved of inestimable value in the treatment of infections of the urinary tract.

In those cases in which the infection cannot be eradicated by chemotherapy, a thorough and complete search by a competent urologist should be advised because of the frequent association of complicating pathologic conditions such as stone, tumor, obstruction or cicatricial deformity.

A moderate sized dose is all that is needed in the treatment of most urologic infections.

The closest observation of patients taking these drugs is needed. The use of the sulfonamide compounds in the treatment of infection of the urinary tract is still in its early stages and true evaluation will necessitate continued experimental and clinical work in order to determine their efficacy in infections of certain types produced by the various organisms.

Council on Physical Therapy

THE COUNCIL ON PHYSICAL THERAPY HAS AUTHORIZED PUBLICATION OF THE FOLLOWING REPORT. HOWARD A. CARTER, Secretary.

McCURDY MODEL GAS MACHINE ACCEPTABLE

Manufacturer: Safety Gas Machine Company, Inc., 1163 Sedgwick Street, Chicago.

The McCurdy Model Gas Machine is designed for the administration of inhalation anesthesia, utilizing D cylinders of oxygen, carbon dioxide, nitrous oxide and ethylene with provision for an extra tank of each gas to be attached to the machine. An efficient reducing valve is connected with the yokes for each cylinder. Leaks from cylinder to cylinder cannot occur. The Augustana Model Gas Machine made by the same manufacturer, which is on the Council's list of accepted devices, is similar to the McCurdy Gas Machine.

McCurdy Model Gas Machine.

Gases are admitted for delivery singly or in combination into a central mixing chamber through individual visible water manometer gages. The flow of each gas may be regulated by individual needle valves to obtain the desired proportion. The graduations on the manometers are apparently in gallons per hour.

A large lever on the top of the mixing chamber may be moved from the "on" to the "off" position if it is desired to by-pass the flowmeters for all gases. In the "on" position, needle valves on the top of the mixing chamber are used to regulate flow. In the "off" position, coarse flow valves on the base of the machine regulate the flow, without any registration of volume by the flowmeters. Apparently the latter provision is to enable the administrator to obtain the larger volumes necessary when using the apparatus for a semiclosed administration of gases, with the flutter valve in the circuit open to allow for exhalation.

A by-pass valve provides a quick source of oxygen. An ether vaporizer which is attached near the outflow from the machine permits the addition of varying percentages of ether to the gas mixture.

The remainder of the apparatus consists of a so-called circle filter or a carbon dioxide absorption unit. The large canister in the circuit may be cut out at will, and an exhalation valve in the circuit may be kept closed for completely closed technic or opened for semiclosed technic.

The mask furnished with this machine is a transparent plastic type with rubber cushion for comfort and good fit. The breathing bag is of about 10 liters capacity. The whole apparatus rests on a substantial pedestal with rubber tired casters. A length of chain attached to the base trails on the floor, apparently for grounding purposes. The apparatus moves readily in spite of its weight.

The resistance to breathing is in the order of 3.5 cm. of water both on inspiration and on expiration, which is comparable to that found in most circle filters and is accounted for by the length of tubing and the inherent resistance to movement of the type of one-way valves incorporated. This resistance might be of some significance during anesthetization of a debilitated individual, especially during a long operation. It is doubtful whether any decrease in resistance could be obtained except by some radically different method of circulating gases.

Absorption of carbon dioxide is quite efficient, as shown by actual gas analysis; that is, compared to other circle filters and to and fro filters which we have tested. It must be recognized that no absorption units in use today reduce carbon dioxide to atmospheric levels.

The Council's clinical investigation revealed that in the hands of the skilled anesthetist the aforementioned gases and their combinations with ether may be efficiently administered with the McCurdy Model Gas Machine.

The Council voted to accept the McCurdy Model Gas Machine for inclusion on its list of accepted devices.

Council on Pharmacy and Chemistry

REPORTS OF THE COUNCIL

THE COUNCIL HAS AUTHORIZED PUBLICATION OF THE FOLLOWING REPORT.

PAUL NICHOLAS LEECH, Secretary.

ORGANIC MERCURIAL COMPOUNDS AS BACTERICIDAL AGENTS

Although mercury, as simple and as complex compounds, has enjoyed popular use for the destruction of bacteria since the time of Koch, there is still no uniformity of opinion as to its true value. Whether this has arisen from lack of adequate controls or from misinterpretation of reported results, the fact remains that simple and complex mercury compounds still enjoy widespread popularity and enormous quantities are sold yearly.

In 1881 Koch reported that mercury bichloride was an effective agent in destroying the spores of even the most resistant bacteria, but in 1889 Geppert showed that the substance was poorly bactericidal but markedly bacteriostatic. In spite of the carefully controlled work of Geppert, mercury bichloride has remained in constant demand, and as each new mercurial is advanced for its antibacterial effects there is a renewed interest, often accompanied by an increasing false sense of security. In recent years solutions of mercurial compounds in which mercury has been combined with dye or other organic radicals have been advocated; because of their popularity they have largely replaced mercury bichloride, mercuric cyanide and mercuric iodide (or potassium mercuric iodide) for their reaction against infective agents; but even reports on these newer agents are not in harmony.

DEFINITION OF TERMS

No doubt one of the reasons for the existing confusion lies in the looseness with which such terms as "antiseptic," "sterilize," "germicide" and "bactericide" are used. According to an editorial which appeared in THE JOURNAL in 1927, a germicide is defined in current medical textbooks as a "substance or agent that destroys micro-organisms so that they will not grow when placed in appropriate culture mediums"; an antiseptic is defined as a "substance that hinders or prevents the growth of micro-organisms but does not necessarily destroy their vitality."

As long ago as 1910 the Council on Pharmacy and Chemistry asserted that:

> It seems of the greatest importance that antiseptic power be not mistaken for germicidal power and that physicians should be correctly informed as to these properties of disinfectants recommended to them, so that they may decide for themselves in every given case which action they wish to produce.

The term sterilization is often used, even by the physician, to connote germicidal or bactericidal or sometimes just bacteriostatic properties. In 1936 the Council formally went on record as "disapproving of the use of the terms 'sterile,' 'sterilize' and 'sterilization' in a bacteriologic sense other than in their correct scientific significance; i. e., meaning the absence or destruction of all micro-organisms." Many feel that they are "sterilizing" an instrument by immersing it for a definite period of time in some mercurial solution. Such an assumption is not necessarily valid, as no evidence has yet been offered [1] which is conclusive and accepted by all that there exists any mercurial compound which can be relied on to destroy the spores of anaerobic bacteria. Limitation exists even with nonsporulating bacteria.

About thirteen years ago the U. S. Bureau of Chemistry, which at that time was charged with the enforcement of the Food and Drug Act, came to the conclusion that the term "antiseptic," when used in the labeling of a medicinal product, was objectionable unless the preparation when used as directed would actually destroy micro-organisms. The Council on Pharmacy and Chemistry regards an antiseptic as having more disinfectant than germicidal properties and not to be necessarily highly germicidal.

In the Insecticide-Disinfectant Code [2] a disinfectant is defined as follows:

> The term disinfectant as used herein means any chemical or drug or combination of chemicals or drugs intended to destroy one or more kinds of disease germs or other harmful micro-organisms (not including bacterial spores) when applied to all inanimate objects that might harbor disease germs.

EVALUATION BY THE PHENOL COEFFICIENT AND OTHER TESTS

Another factor which has been of little service in clarifying the picture is the use of the phenol coefficient test as a method of evaluating the antibacterial properties of the mercurials. Attention was drawn to this by the Council in a report of its 1939 annual meeting [3] when the members cited the following paragraphs from circular 198 of the U. S. Department of Agriculture:

> There are certain types of germicidal agents, such as many of the mercury compounds, which give very high results by phenol coefficient tests. Due to the high inhibitory value of such substances in preventing growth in the subcultures, these figures are frequently misleading. For germicides used in the disinfection of such objects as surgical instruments, this is of particular importance and must be taken into account. Failure to appreciate this characteristic of certain compounds is much more likely to lead to error when Staphylococcus aureus is used rather than Eberthella typhi as the test organism. That false values may not be obtained for products of this type, or for any other disinfectant giving suspiciously high results, the subcultures should contain very large amounts of medium or they should be retransferred by carrying at least four loopfuls from the first subculture to a second tube of broth, as recommended by Shippen.
>
> Other groups of disinfectants in common use, for which the phenol coefficient method of testing is not well adapted, are those compounds containing chlorine as the active agent, as well as the oxidizing agents in general. These are affected so materially by the presence of organic matter that a phenol coefficient statement may grossly misrepresent their value under practical conditions of use and is very apt to be misleading to the consumer when placed on the label.

The Council pointed out that an unduly high and misleading phenol coefficient is given in the case of mercurial disinfectants because the retransfer method was omitted, and any bacteriologic

1. Brewer, J. H.: The Antibacterial Effects of Organic Mercurial Compounds, J. A. M. A. **112**: 2009 (May 20) 1939.
2. Insecticide-Disinfectant Code, Soap **10**: 81, 1934.
3. Annual Meeting of the Council on Pharmacy and Chemistry, J. A. M. A. **112**: 2277 (June 3) 1939.

tests for mercurial compounds alleging bactericidal properties should be made under conditions of actual application to supplement a test under simplified and arbitrary conditions. For instance, it has been found that mercurials are rendered completely inert bacteriologically by the addition of relatively larger amounts of normal horse serum. To get a therapeutic result even in serum would require many times the lethal dose of the mercurial. This inactivation by serum has been studied quantitatively by Smith, Czarnetzky and Mudd.[4] In view of such reports, the Council declared the phenol coefficient to be an inadequate basis for judging the antiseptic value of nonphenolic agents needing to be supplemented by tests under conditions of actual use.

The principle of the phenol coefficient test used in 1903 by Rideal and Walker is essentially that employed at present. The phenol coefficient is that figure which is obtained on dividing the greatest dilution of the disinfectant killing test organisms in a definite period of time by the greatest dilution of phenol killing in the same interval of time. There have been many attempts to improve on the original method but none have attained perfection. Knighton[5] compared the Hygienic Laboratory method and the Food and Drug Administration phenol coefficient method with the Rideal and Walker method and demonstrated the variations in technic designed to simulate practical conditions. In addition, he reviewed other variations such as using different test organisms, adding sterilized fecal material and serum, wet and dry filter paper method, agar plate method and agar cup plate test. Not one has proved to be ideal.

Since the phenol coefficient test is of dependable value only for comparison of the efficiency of phenol and phenol-like compounds and does not take into account the destruction of bacterial spores or the part which organic material may play, various totally different procedures have been devised[6] but little more success has been met, since in vitro experiments will not necessarily give the same experimental results in vivo or even when repeated in vitro.

Many tests are misleading because of misinterpretation of the results. According to Knighton,[5] some of the faults are due to (*a*) comparing the usable dilution with the germicidal strength, (*b*) testing the material on only one or two types of organisms or, in the case of spore-forming bacteria, on the organisms in their vegetative form rather than on the spores, (*c*) failing to account for possible deterioration in volatile substances, (*d*) ignoring the fact that certain chemicals may behave differently when diluted or when combination occurs with other substances which are present, (*e*) confusion of terminology and (*f*) lack of appreciation, especially with the mercurial compounds, of the bacteriostatic substances giving exaggerated bactericidal value when the phenol coefficient test is used. Neutralization of the inhibiting factor by subculture, washing or a neutralizing agent must first be carried out to prevent false bactericidal values.

Thaysen[7] criticized the British Standards Institution's technic of the Rideal-Walker test for the evaluation of antiseptics because of difficulties in obtaining consistent results which arise from the survival of a few of the bacteria when exposed to the solution to be tested. Transference of at least one cell to the growth tubes may be problematic on account of a too small number of surviving cells. To ensure transfer of the organisms would require transfer of much larger quantities of the solution than is required by the test. The British Standards Institution test requires an exposure of eight minutes, the Chick-Martin test an exposure of thirty minutes. However, the latter gives more consistent results than the Rideal-Walker test with a ten minute exposure. Complete destruction of Bacterium typhosum in phenol solutions requires one hour.

Apart from the lack of accurate tests for determining the true comparative bactericidal value of compounds in test tubes there remains the fact that any antibacterial effect observed in vitro will not necessarily be the same on living tissue. Factors here which will determine the eventual outcome include bactericidal action of normal blood, previous history of disease, type of organism, virulence, number of organisms present, presence of organic material and the tissue toxicity of the antibacterial agent. Because of the part played by phagocytosis in combating infection, Welch and Hunter[8] made use of this phenomenon in developing a method of testing antiseptics by determining what they called a toxicity index, which is the highest dilution of antiseptic toxic for tissue (determined by the inhibition of phagocytosis) divided by the highest dilution capable of killing the test organism. This procedure is remindful of that performed by Salle and his associates,[9] who determined a toxicity index by using chick embryo tissue. A summary of the tissue toxicity tests has been made by Knighton[5] in an attempt to point out that there is a need for tests to determine any deleterious effect on the skin, as well as the relative efficiency of the substance tested.

Another factor which may influence the effectiveness of a germicide is the acidity. Bittenbender and his co-workers[10] point out that acidity has been known since the time of Pasteur to affect the growth of some bacteria. Previous work[11] showed that a change in hydrogen ion concentration affected the action of some organic mercury compounds, phenolic compounds and other antibacterial agents. This work was confirmed by Bittenbender[10] using Staphylococcus aureus and Escherichia coli as test organisms. The agents showed increased potency with an increase in the hydrogen ion concentration of the medium.

Rose and Miller[12] concur with the observations which suggest that test tube experiments give no true indication of the effectiveness of an antiseptic or germicide when applied to tissues or when mixed with blood, saliva and exudates. They studied certain mercurials in the presence of from 1 to 50 per cent blood solution with Staphylococcus aureus as the test organism and found that increase in blood concentration decreased antiseptic effectiveness by using the formula $C = Ke\text{-}mz$, where C = concentration of blood (%), K = a constant for each antiseptic, e = base of naperian logarithms, m = coefficient of inactivation of the antiseptic and z = zone of inhibition of bacterial growth (mm.). It was concluded that the mercurials have no antiseptic action at certain critical blood levels. Hunt[13] injected a strain of Staphylococcus aureus intravenously into mice and found that mercurial compounds failed to prevent infection or lessen necrosis if mixed with the bacterial suspension just before injection.

MODE OF ACTION

According to Brewer[1] the most generally accepted ideas regarding the manner in which the mercurials show antibacterial properties probably arise because mercury bichloride was known to coagulate the proteins by a direct combination with the tissues. It is now more or less believed that the mercurials precipitate bacterial protein. Modifications of this view, together with the surface absorption and enzyme destruction theories, have been reviewed by Brewer, but in conclusion he admits that not one of the suggested theories has offered a complete and satisfactory explanation.

4. Smith, D. E.; Czarnetzky, E. J., and Mudd, Stuart: The Mechanism of Inactivation of Mercurial Antiseptics by Serum, and Its Implications Regarding the Possibility of Intravenous Antisepsis, Am. J. M. Sc. **192:** 790 (Dec.) 1936.

5. Knighton, H. T.: Significance of Tests for Evaluation of Antiseptics and Germicides, J. Am. Dent. A. **26:** 2047 (Dec.) 1939.

6. Peterson, J. B.: Mercurials: A Proposed Method of Laboratory Evaluation and Classification, J. A. M. A. **87:** 223 (July 24) 1926. Welch and Hunter.[8] Novak and Hall.[10] Brewer.[1] Knighton.[5]

7. Thaysen, A. C.: Some Observations on the Rideal-Walker Test, J. Hyg. **38:** 558 (Sept.) 1938.

8. Welch, Henry, and Hunter, A. C.: Method for Determining the Effect of Chemical Antisepsis on Phagocytosis, Am. J. Public Health **30:** 129 (Feb.) 1940.

9. Salle, A. J.; McOmie, W. A.; Shechmeister, I. L., and Foord, D. C.: Evaluation of Group of Germicides by Tissue Culture Technic, J. Bact. **37:** 639 (June) 1939.

10. Bittenbender, W. A.; Degering, E. F.; Tetrault, P. A.; Feasly, C. F., and Gwynn, B. H.: Bactericidal Properties of Commercial Antiseptics: A Further Study of the Effect of *p*H, Indust. & Engin. Chem. **32:** 996 (July) 1940.

11. Goshorn, R. H.; Degering, E. F., and Tetrault, P. A.: Antiseptic and Bactericidal Action of Benzoic Acid and Inorganic Salts: Effect of *p*H, Industrial. & Engin. Chem. **30:** 646 (June) 1938.

12. Rose, S. B., and Miller, R. E.: Studies with the Agar Cup-Plate Medium: II. The Effect of Blood on Mercury Antiseptics, Am. J. M. Sc. **199:** 338 (March) 1940.

13. Hunt, G. A.: Use of Cutaneous Staphylococcus Lesions in Mice for Evaluation of Germicidal Activity of Disinfectants, J. Infect. Dis. **60:** 232 (March-April) 1937.

In 1917 Sollmann [14] reported that it was difficult to kill bacteria on body surfaces because solutions which are definitely germicidal might destroy the tissues, and because chemical antiseptics are weakened by the presence of organic matter. If, however, it is possible to injure the bacteria in some manner, the injury may be enough to effect subsequent death of the bacteria either as a direct result of the cell injury or by aid of the tissue reactions.

Actual injury to the bacteria which have managed to get within the body tissues is even more difficult, since organic matter may be precipitated and hinder further any tissue penetration by the germicide that might conceivably occur.

COMPARATIVE VALUE

The efficiency of chemical disinfecting or germicidal agents is largely dependent on the form and material of objects to be sterilized. Attempted sterilization of utensils by chemical agents involves employment not only of solutions that are actually bactericidal but also of methods which ensure adequate contact between bacteria and solution. The latter is the more difficult part of the problem. Because the market is flooded with chemical agents which are as effective bacterially as or even better than a standard solution of phenol in ideal laboratory conditions, it does not necessarily follow that the same pathogenic organisms will be destroyed on instruments or skin which are protected by coatings of organic material whether it is dried mucus, coagulum or just grease and dirt.

Novak and Hall [15] found an average of twelve staphylococci and diphtheroids per square centimeter on what was normally considered clean skin. Application of 50 per cent alcohol and 10 per cent acetone solution, a common solvent for antiseptics, destroyed 95 per cent of the bacteria on the skin. Only from 2 to 3 per cent more were killed when any commonly used skin antiseptic was added to this solvent. Tincture of green soap alone killed only 53 per cent of the skin bacteria. When skin antisepsis is desired, it is necessary to consider not only resident bacteria but also any transient bacteria that may be present. The same strains of an organism may show individual variation under different cultural environments.

Bass [16] reviewed some of the previous literature and left open the suggestion that some of the antibacterial action attributed to the mercurials might be due to bacteriostasis. Using adult rabbits for experimentation with Birkhaug's method, which was reported in 1933, Bass tested a series of the more common agents. Using 70 per cent ethyl alcohol as a standard of comparison, which sterilized 27.7 per cent of skin areas treated, he found that sterilization of the skin by other agents ranged from 38 to 80 per cent. He found evidence that some of the newer organic preparations of mercury were of distinct value as antiseptics and possessed more germicidal activity than the older chlorides of mercury, but absolute sterilization was never obtained. Price [17] has reported that 70 per cent by weight of ethyl alcohol is the most effective concentration of alcohol for antibacterial properties. Slight variations from this percentage lessens the bactericidal action. From his observations he evolved a simple technic for preoperative cleansing of the hands and arms. Essentially it consists of scrubbing the hands and arms with a brush, soap and warm water for seven minutes, drying them with a sterile towel, rinsing in 95 per cent alcohol to remove any remaining water, and then washing for three minutes in a basin well filled with 70 per cent alcohol (by weight). Later investigations by Price [18] also revealed information on the germicidal values of mercury bichloride and of potassium mercuric iodide. When skin free of grease is washed in one of these mercurials there is formed a sterile impermeable "film" which protects the underlying cutaneous bacteria. This "film" is impervious to bacteria, slightly permeable to alcohol and very resistant to friction. However, beneath the "film" the bacteria are unharmed and multiply at a rapid rate. The formation of such a "film" probably explains why the older surgeons often enjoyed relative asepsis when operating without gloves. Price believes that mercury bichloride and potassium mercuric iodide (1 : 500) are of value in preoperative disinfection of the hands whenever an ungloved hand must be used in obstetrics or surgery. These agents may also have a place in the preparation of the field of operation but should not be depended on to effect sterilization at the site through which an incision is to be made.

Older forms of mercury, such as the bichloride, in addition to not killing spores on instruments, corrode the metal and may cause dermatitis when in prolonged contact with the skin. Because of their toxicity when injected parenterally, they could not be used in chemotherapy. About the close of the World War the first organic mercurials appeared with great claims for ability actually to sterilize instruments. However, these claims lacked support by way of adequate tests. Their inability to sterilize sutures was reported by Brewer,[19] while making a survey for the Council on Pharmacy and Chemistry.

Examination by the Chemical Laboratory of the American Medical Association has revealed that decomposition with the liberation of free mercury of many organic mercurials occurs on standing. The preparations examined included solutions in ampules, lubricating jellies and creams. This work appears to indicate that the organic mercurials are not sufficiently stable to prevent partial disintegration from occurring over varying periods of time.

CONCLUSION

Mercurial preparations are used for antiseptic and disinfecting purposes, but they cannot be expected to destroy spores after several hours' exposure or even be relied on to destroy some nonsporulating bacteria. The organic compounds of mercury are claimed, in general, to be less irritating and less toxic than the older preparations of mercury, but their germicidal activity is in doubt in many instances, even though they may, and often do, have a highly bacteriostatic value. Because of their bacteriostatic ability the organic mercurials are of value as first aid prophylactic antiseptics and as preservatives of certain biologicals for parenteral use. Claims for their ability to penetrate deeply into living tissue and to act as chemotherapeutic agents have yet to be adequately supported.

Sterilization of contaminated instruments and dishes, whether by autoclaving, boiling water or live steam, is more simple, fairly rapid, inexpensive and more certain than by any chemical method known at the present time. Once the material is sterilized and kept dry in an airtight container, it will remain sterile for a considerable period.

It is thus apparent that the organic mercurials can be used for certain bacteriostatic purposes and in some instances for bactericidal effects. However, they cannot be expected to destroy pathogenic spores, and even their action on nonsporulating bacteria is limited. Skin sepsis is best prevented by a thorough cleansing with soap and water and a solvent such as alcohol and acetone before using any antiseptic agent. At present, ethyl alcohol (70 per cent by weight) appears to be one of the most reliable antibacterial agents.[20]

No safe organic mercurial compound has yet been offered which will guarantee destruction of spores in suture material.

14. Sollmann, Torald: The Actions of Drugs, Philadelphia, W. B. Saunders Company, 1917.

15. Novak, Milan, and Hall, Harry: Method for Determining Efficiency of Preoperative Skin Sterilization, Surgery **5:** 560 (April) 1939.

16. Bass, A. D.: An Experimental Comparison of Certain "Skin-Sterilizing" Agents, J. Pharmacol. & Exper. **66:** 279 (July) 1939.

17. Price, P. B.: Ethyl Alcohol as a Germicide, Arch. Surg. **38:** 528 (March) 1939.

18. Price, P. B.: Mercuric Chloride, Potassium Mercuric Iodide and Harrington's Solution in Skin Disinfection, Surg., Gynec. & Obst. **69:** 5946 (Nov.) 1939.

19. Brewer, J. H.: The Present Status of Sterility of Catgut Sutures on the American Market, J. A. M. A. **108:** 722 (Feb. 27) 1937.

20. In practice, the amount of alcohol in a preparation is generally referred to in terms of per cent by volume. Certain regulations in pharmaceutical practice state that the per cent of alcohol always means "by volume," unless expressed in terms by weight. As ethyl alcohol U. S. P. varies somewhat in water content, generally from 94 to 95 per cent by volume, it is impossible to give a definite formula for preparing alcohol 70 per cent by weight. Probably the best method would be to add approximately 25 cc. of water to 100 cc. of alcohol and adjusting the mixture so that the specific gravity at a temperature of 25 C. is 0.8658. A stock solution may be checked by determining the specific gravity. Alcoholometric tables appear in many books of analysis, and an official table appears in the U. S. P. XI. A Westphal balance, or a well graduated hydrometer, is satisfactory for determining specific gravity.

THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

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SATURDAY, DECEMBER 14, 1940

AMERICAN COLLEGE OF SURGEONS JOINS FORCES WITH AMERICAN MEDICAL ASSOCIATION IN HOSPITAL CENSUS

Each year the Council on Medical Education and Hospitals of the American Medical Association takes a census of registered hospitals, numbering more than 6,000. The American College of Surgeons also has obtained statistical reports from hospitals already meeting the minimum standards of the College and those under consideration for approval. The combination of these reports into one simplified form will be welcome to the hospitals and especially to their administrative officers. Printed in triplicate, a single typing of the form supplies a report for each of the interested organizations and provides a carbon copy for the files of the hospital. All forms are coded for punch card tabulation. Thus, with a minimum of trouble and expense, both the College and the Council secure such information as is necessary for the continuance of their recognition. Also the compiled returns serve as a basis for the Hospital Number of THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, which places essential information in the hands of all hospitals, physicians and others concerned. This should render unnecessary many of the questionnaires now sent to hospitals.

It is gratifying to record that the returns are coming in more promptly than in other years and that over 50 per cent of them were received within ten working days after mailing. Hospitals that have not yet responded should do so at once. Staff physicians can do a good turn by asking at the office whether the report has been completed and mailed.

The hospitals approved for the training of interns and residents will receive their questionnaires late in December so that the reports may cover the calendar year 1940.

The combined census is one feature of the program for increased cooperation between the American Medical Association and the American College of Surgeons. Another phase of this get-together movement is the coordination of hospital inspection so as to avoid duplication and extend inspection service for hospitals.

WAR MEDICINE—A NEW PUBLICATION

Beginning in January, the American Medical Association will publish a new periodical: "WAR MEDICINE," as a part of its contribution to the preparedness program. The editorial board of the publication will be the Committee on Information of the Division of Medical Sciences of the National Research Council. This committee includes Dr. Morris Fishbein, Editor of THE JOURNAL, as chairman, and the following associate editors: Mr. J. R. Bloomfield and Drs. John F. Fulton, Richard M. Hewitt, Ira V. Hiscock, Sanford V. Larkey and Robert N. Nye. In order to have direct cooperation with the governmental services, the following representatives of the Army and Navy Medical Corps and the United States Public Health Service have been chosen to cooperate with this editorial board: Col. C. C. Hillman, Com. Charles S. Stephenson and Dr. R. R. Spencer.

The Division of Medical Sciences of the National Research Council has developed a number of scientific committees which are actively at work preparing reports of various phases of medical service under military conditions. These official documents will be available to the new periodical for prompt publication. Already reports on chemotherapy, the standardization of the treatment of pneumonia, numerous problems concerned with medicine in aviation, peripheral nerve injuries, wound treatment, gas gangrene and similar subjects are being made available.

The American Medical Association, through its Committee on Medical Preparedness, is concerning itself with all the questions of personnel for preparedness and for military service. The official reports of this committee will also appear in the new periodical as well as special considerations that are given to economic and social problems of the medical profession in relationship to the emergency. Of especial importance also are the reports of official committees of the American Medical Association, such as the Council on Medical Education and Hospitals, the Council on Industrial Health and similar groups which will also be concerned with these problems.

Finally, much material is being developed by the Coordinating Committee on Medicine and Health of the Council of National Defense and by many other governmental agencies which are considering the national nutrition, the provision of hospital services and similar questions closely related to preparedness and defense.

The new publication will appear as a bimonthly. The Board of Trustees of the American Medical Associa-

tion, which has authorized its publication, has established a price of $5 annually for the subscription. The periodical should be useful not only to the government services, which have indicated their wish to subscribe to this periodical for their official departments, but also to libraries and to individual physicians.

THE INDUSTRIAL NURSE

Competent industrial health service depends on the availability of physicians adequately trained in industrial medicine, hygiene and traumatic surgery. Ordinarily, however, assistance is necessary from other properly qualified professional personnel. Industrial medical departments provide excellent opportunities to nurses with proper aptitude, good comprehension of public health nursing methods and a sure sense of their own professional limitations. A clinical and administrative assistant of this character will be of immense aid to any industrial physician in the performance of many routine functions which make up the bulk of industrial dispensary procedure. The system works admirably under whole-time industrial physicians or under part-time physicians who spend regular visiting hours at a plant. In the absence of direct medical supervision, written standing orders, properly posted in the plant medical unit, will do much to inhibit assumption of services which require expert medical attention. Unfortunately, many of the smaller plants which have found it possible to arrange for some form of nursing service fail to recognize the need for such supervision or consider themselves unable to support even part-time medical aid. A nurse working under such conditions acts under heavy professional and ethical handicaps. Some form of medical supervisory arrangement is necessary to provide nurses with technical advice. The physicians on call for first aid and compensation work may be most helpful, particularly if they have some insight into the actual working environment. Committees on industrial health now being formed in county medical socities will find the industrial nursing field a fertile one for helpful and cooperative activity, both in a direct advisory capacity and as coordinators of private and public medical services. Frequently they may be called to correct unhealthful industrial situations which the nurse uncovers. Unified service of this kind is already contemplated, using the part-time services of public health or visiting nurses paid for by small industry on a fee basis calculated according to hours per week required.

These relationships are particularly pertinent in view of the speeding up and intensification of industry that is occurring as part of the preparedness program. Many more nurses will be needed than are now available. They can make a valuable contribution to industry by supplying first aid and nursing care to plant personnel, assisting the physician in health examinations, and helping the worker to secure correction of defects through reference to the family physician or other properly designated medical agency. The nurse is concerned with sanitary conditions within the plant and may in many ways promote the health and safety of industrial workers. The nurse should participate in the work of health education in industry and encourage sanitary and hygienic precautions that will diminish absenteeism due to illness and accident.

New requirements for industrial health service will demand much more trained personnel than is now available. Schools of nursing should concern themselves at once with courses in industrial hygiene not only to undergraduate but to graduate students. Better education regarding industrial hazards, industrial relationships and the principles of health organization will encourage industrialists to extend their employment of good industrial nursing services. The need for higher standards is well recognized by leaders in the nursing profession, and plans are currently under discussion for additional improvement. Community of interest is so great that no opportunity should be lost by the medical profession to assist the industrial nurse, individually and collectively, to elevate her professional status.

PROPOSED ADDITIONS TO AND DELETIONS FROM THE NEXT UNITED STATES PHARMACOPEIA

The new Revision Committee of the U. S. Pharmacopeia has already begun to consider recommendations on scope. A number of important policies were adopted at the 1940 U. S. Pharmacopeial Convention which apparently will be reflected in the type of articles to be included or deleted from the next revision. Because of the importance of the Pharmacopeia to the practice of medicine, the U. S. P. Subcommittee on Scope has wisely prepared a preliminary statement of the suggested changes. Both physicians and pharmacists should consider the proposals, and discussions may well be presented in the pharmaceutic and medical press. The president of the Pharmacopeial Convention and the chairman of the Subcommittee on Scope have outlined the policy under which medicinal substances have been admitted to the Pharmacopeia:

> The Subcommittee on Scope, which decides admissions and deletions for a new Pharmacopeia, is primarily responsible for the value and usefulness of the book to the medical profession. The fundamental medical and pharmaceutical objectives of the Pharmacopeia from the time it was established have been to include a selected list of the best known and most thoroughly tested medicines of each revision period and also suitable usage or dosage forms or preparations of these important basic medicines. It has always been the aim of those responsible for the Pharmacopeia that it should be so comprehensive as to meet every need of medical practice, insofar as there are efficient medicinal products and medical aids known and available.
>
> This principle of Pharmacopeial admissions has been maintained and practiced since 1820 and was emphatically reaffirmed by the Subcommittee on Scope during the recent meeting of the Committee of Revision. When it is determined that a medicinal substance or preparation fails to meet the standard of therapeutic excellence or service required by the Revision

Committee or when a patent situation intervenes, such a substance, or preparation, is denied admission to the Pharmacopeia. This policy of the Pharmacopeia of the United States is the basic policy for all pharmacopeias of the world. Under it is included any substance or preparation used in medicine which in the opinion of its experts is worthy of Pharmacopeial recognition. Under this accepted policy, the Pharmacopeia has been able to develop and maintain a unique voluntary service to medicine, pharmacy and the public, a contribution recognized and accepted by the medical and associated professions, and the manufacturing drug industry, and adopted by state and federal legislation.

Fifty-five additional products have been recommended for inclusion in the new Pharmacopeia, a few simply as pharmaceutic necessities. In addition, thirty or more substances have been recommended for inclusion, but because of trademark or patent involvements the names have been withheld until the committee has opportunity to give them further study and to discuss the question of proprietorship with the owners of the trademarks and patents. Elsewhere in this issue (see page 2110) may be found a list of additions and also a list containing titles of the products which the committee recommends to be deleted. The recommendations of the committee show constructive effort. On some items there may be a difference of opinion, particularly whether or not the products are sufficiently established to be recognized in the Pharmacopeia for purposes of use by the general practitioner.

Nomenclature of these products will be dealt with by another committee, which has indicated that, wherever possible, established nonproprietary terms will be used. The titles in themselves, as they appear in the present list, do not imply that the respective names are to be considered as final.

THE PROBLEM OF PSITTACOSIS

Psittacosis is primarily a disease of so-called psittacine birds such as parrots and parrakeets. The disease is transmissible to man, however, and is characterized by high fever associated with symptoms of an atypical pneumonia. Occasionally the disease can be transmitted from man to man, but the most common source of human infection is from parrots and parrakeets which have been kept as household pets. No doubt many infected birds will be distributed as Christmas presents, and the hazard at this time demands a warning.

Meyer and his colleagues [1] at the Hooper Foundation in San Francisco have been persistent in their research on this disease. Much information on the nature of the virus which causes psittacosis is now available. On the basis of ultrafiltration measurements verified by photomicrographic studies it has been determined that the infective particle of psittacosis has a minimum size of from 0.2 to 0.3 micron. Furthermore the infective agent of psittacosis has been shown to be the elementary body itself and not a separable substance or an invisible particle of the same size. The virus can be satisfactorily cultivated on the chorioallantoic membrane of the developing egg. Agglutinins for the elementary bodies of psittacosis have been produced experimentally in guinea pigs, and control experiments have proved that the agglutination reaction resulting was not due to the presence of foreign protein or virus contamination. Indeed, the virus of psittacosis as represented by the elementary bodies acts in all respects as a small micro-organism requiring an intracellular habitat for multiplication and survival. The particular value of the serologic investigations, however, resides in the fact that they have led to the demonstration that complement fixation tests with cocto antigens prepared from virulent mouse spleens or Rivers-Li tissue cultures of the virus are specific in nature and serve as invaluable aids in the early and late diagnosis of human psittacosis. Preliminary observations indicate that either convalescent serum or a highly potent goat serum which has been produced may shorten the course of the human disease. A specific test is therefore available and new potentials for treatment are in sight.

Psittacosis is widely distributed among birds in this country. In one shipment of 161 parrots, parrotlets and conures from South America, Meyer and Eddy examined 158 following the preceding death of 3 of the birds. Both the Panama parrots and the macaws presented gross lesions of psittacosis in the form of emaciation and large spleens and livers with healed necroses. In fact, of the whole group only 15 parrotlets and 1 Wagner parrot were proved free of the virus of psittacosis. Similar high incidence of infection was found in shipments from Colombia and Australia.

Such high percentages of infection of imported birds for house pets underline the danger of wide distribution of human disease, and some effective means of eliminating the diseased birds is of great importance. One method employed has been to introduce the rice bird into new shipments of psittacine birds. This bird has been found susceptible to the virus and is ideal in certain respects for experiments. This exposure method, however, requires an observation period of not less than two to three months and might fail to answer the pertinent questions relative to latent psittacosis in the imported birds. In later experiments from 5 to 10 cc. of blood (depending on the size of the parrot) was withdrawn from the superficial ulnar vein without difficulty, provided the birds had been properly anesthetized with ether. The concentrated tissue culture in Rivers-Li medium was used in the preparation of antigens, and complement fixation reactions were performed according to a somewhat complex technic. These complement fixation reactions could be interpreted as indicative of previous contact of the parrots

1. Lazarus, A. S., and Meyer, K. F.: The Virus of Psittacosis, J. Bact. **38**: 121 (Aug.) 1939. Meyer, K. F., and Eddie, Bernice U.: Psittacosis in Importations of Psittacine Birds from the South American and Australian Continent, J. Infect. Dis. **65**: 234 (Nov.-Dec.) 1939; The Value of the Complement Fixation Test in the Diagnosis of Psittacosis, ibid. **65**: 225 (Nov.-Dec.) 1939.

with the psittacosis virus. There is little doubt, therefore, that the complement fixation test may prove valuable in detection of the presence of psittacosis in an importation and for separating the healthy from the recovered birds. Others [2] have confirmed the value of the test. The complement fixation test, besides its function in birds, has also proved its usefulness as a diagnostic aid in human psittacosis both early and late. Further laboratory investigations aimed at improvement and refinement of technics are indicated and the development of a more effective specific method of treating the disease in man. Most promising at present is the use of convalescent serum and goat serum.

THERAPEUTIC TRIALS WITH RADIOACTIVE PHOSPHORUS

Several radioactive substances with possibilities for medical application have been prepared with the use of the cyclotron. Up to now radioactive phosphorus has been tried therapeutically more than any other element. Phosphorus, artificially made radioactive, appears to be especially interesting because it is easily manufactured in the cyclotron, because its half-life is relatively long, 14.8 days, and because phosphorus is important in organic and inorganic metabolism generally. Its essential difference from natural inactive phosphorus, according to Lawrence and his co-workers,[1] resides in the fact that its nucleus contains an extra neutron and it emits beta rays (electrons) when administered in the form of sodium phosphate. Bone eventually would be expected to retain a larger percentage than any other tissue, and bone, with such a high phosphorus content, would get the greatest number of radioactive atoms per gram. From studies on leukemia in mice it was considered possible that the administration of large quantities of radiophosphorus would seem to offer a method of getting more or less selective radiation in this disease. With this basis, Lawrence and his colleagues carried out metabolic and clinical studies employing radiophosphorus in six cases of leukemia—one lymphatic, one monocytic and four myelogenous leukemia. Although the clinical results were doubtful, it appeared that decreases in the number of white blood cells occurred in a manner similar to that produced by roentgen irradiation when large doses of radiophosphorus were given to patients with leukemia.

A later report by Lawrence [2] describes five additional cases of chronic myelogenous or chronic lymphatic leukemia treated by the oral administration of radiophosphorus in the form of sodium phosphate with resultant responses similar to those usually following roentgen or radium therapy. Two additional cases of polycythemia vera were also reported in which similar treatment resulted in a fall in the hemoglobin, red blood cell count and reticulocyte count without evident destruction of the red blood cells. The principal advantages of this treatment according to Lawrence are that it offers a means of giving the whole body radiation continuously over a period of two or more weeks in a single oral dose of sodium phosphate, and there are no irradiation reactions.

Warren's [3] report on the treatment of leukemia by radioactive phosphorus—just published—involved the study of four cases of acute or subacute leukemia. Most of the radioactive phosphorus used in the treatment of these cases was obtained from the Harvard cyclotron and had a half-life of 14.5 days. The desired amount of radioactive phosphorus ranging from one to four millicurie equivalents was dissolved in 5 per cent dextrose and physiologic solution of sodium chloride prepared for intravenous use, sterilized and injected intravenously. The intravenous route of administration was adopted because of the disadvantage of the oral route in that the proportion absorbed by way of the gastrointestinal tract is variable, and frequently over 10 per cent may fail to be absorbed. Two patients showed no significant response beyond minor changes in white cell count, and both subsequently died. In the two others some clinical improvement was noted, as evidenced by the general condition, level of white cell count and condition of bone marrow.

As yet the use of radioactive phosphorus as a therapeutic method is in the preliminary stage: the results offer promise, but important factors remain to be elucidated, including the type and stage of leukemia which might be expected to respond and the dosage and route of administration, both of which are still on a purely arbitrary basis. No doubt further investigation will clarify these points so that radiophosphorus or some other radioactive element can become firmly established as an addition to therapeutic methods.

Current Comment

THE CLEVELAND SESSION

Already the Council on Scientific Assembly has met, local committees are being established, places of meeting have been organized and movement has begun toward the making of a successful session for the American Medical Association in Cleveland, June 2-6, 1941. Elsewhere in this issue appears a table listing the hotels in Cleveland, with the prices that have been established for various types of hotel accommodations. Recent sessions of the American Medical Association have been attended by many thousands of physicians; in fact more than 12,000 registered at the meeting in New York last year. Obviously, it is desirable for every physician who plans to attend the Cleveland ses-

2. Ruys, A. Charlotte; Noordam, A. L., and Vervoort, H.: Psittacosis in Amsterdam Detected with Aid of Complement Fixation Reaction, Nederl. tijdschr. v. geneesk. **83**: 3776 (July 29) 1939.

1. Lawrence, J. H.; Scott, K. G., and Tuttle, L. W.: Studies on Leukemia with the Aid of Radioactive Phosphorus, Internat. Clin. **3**: 33 (Sept.) 1939.

2. Lawrence, J. H.: Nuclear Physics and Therapy: Preliminary Report on a New Method for the Treatment of Leukemia and Polycythemia, Radiology **35**: 51 (July) 1940.

3. Warren, Shields: The Treatment of Leukemia by Radioactive Phosphorus, New England J. Med. **223**: 751 (Nov. 7) 1940.

sion to reserve space as soon as possible. The Hotel Committee in Cleveland is convinced that it will be able to accommodate satisfactorily all physicians who wish to attend, provided some inkling may be obtained soon of the number of physicians who will attend and the type of accommodations which they will require. The cooperation of the medical profession in this matter will insure a greater degree of comfort, a more successful convention and more general satisfaction than can be secured in any other way. If you plan to go to Cleveland, write at once to Dr. Edward F. Kieger, Chairman of the Hotel Committee, Cleveland Convention & Visitors' Bureau, Inc., 1604 Terminal Tower, Cleveland, Ohio, using preferably the blank which appears on advertising page 36 in this issue. Indicate a first, second and third choice of hotel. Indicate whether or not you will require extra space for your wife, your children or any other guests who plan to accompany you.

MEDICAL PREPAREDNESS

In this section of The Journal each week will appear official notices by the Committee on Medical Preparedness of the American Medical Association, announcements by the Surgeon Generals of the Army, Navy and Public Health Service, and other governmental agencies dealing with medical preparedness, and such other information and announcements as will be useful to the medical profession.

COUNCIL OF NATIONAL DEFENSE

Coordination of Health, Welfare and Related Defense Activities

Pursuant to the authority vested in it by section 2 of the Act of Aug. 29, 1916 (39 Stat. 649), the Council of National Defense, with the approval of the President, hereby designates the Federal Security Administrator as Coordinator of all health, medical, welfare, nutrition, recreation and other related fields of activity affecting the national defense. In the performance of this responsibility the Federal Security Administrator as Coordinator shall, in cooperation with the Advisory Commission to the Council of National Defense, formulate and execute plans, policies and programs designed to assure the provision of adequate services of this character to the nation during the national defense emergency; and to that end he shall coordinate the facilities of existing federal agencies with respect to these several fields of action and shall establish and maintain liaison with such other agencies, public or private, as he may deem necessary or desirable.

The Federal Security Administrator is authorized, with the approval of the President, to appoint such advisory committees and subcommittees with respect to health, medical, welfare, nutrition, recreation and related activities as he may find necessary or desirable to assist him in the performance of his coordinating duties. Such committees and subcommittees may include representatives from federal departments and agencies, state and local governments, organized private groups and the public at large. The members of advisory committees and subcommittees shall serve as such without compensation but shall be entitled to actual and necessary transportation, subsistence and other expenses incidental to the performance of their duties. Each committee and subcommittee shall operate under the direction and supervision of the Federal Security Administrator as Coordinator and shall serve at his pleasure.

The Health and Medical Committee established by order of the Council of National Defense, dated Sept. 19, 1940, is hereby transferred to the Federal Security Agency, and such committee shall hereafter exercise its duties and functions under the direction and supervision of the Federal Security Administrator. Vacancies occurring in the membership of this committee shall hereafter be filled by appointment of the Federal Security Administrator, with the approval of the President. All rules and regulations, projects and activities of the committee required to be approved by the Council of National defense or the President shall, prior to submission thereto, be approved by the Federal Security Administrator.

Within the limits of appropriations allocated for purposes encompassed by this order, the Federal Security Administrator may contract with and transfer funds to existing governmental agencies and institutions and may enter into contracts and agreements with individuals or educational or scientific institutions for studies, reports, experimental investigations and expert counsel.

HENRY L. STIMSON,
Secretary of War.

FRANK KNOX,
Secretary of the Navy.

HAROLD L. ICKES,
Secretary of the Interior.

CLAUDE R. WICKARD,
Secretary of Agriculture.

JESSE H. JONES,
Secretary of Commerce.

FRANCES PERKINS,
Secretary of Labor.

Approved:
FRANKLIN D. ROOSEVELT,
Nov. 28, 1940.

GENERAL CONFERENCE ON PSYCHIATRIC EXAMINATIONS

The Director of Selective Service, C. A. Dykstra, invited a number of leading specialists in the treatment of mental disorders to Washington, D. C., December 5, for a general conference on the standardization of psychiatric examinations of Selective Service trainees. On the program of the conference was a proposal to hold a series of conferences throughout the United States which would serve as "refresher" courses for the local board physicians who examine Selective Service registrants when they are called up for physical examination. Mr. Dykstra believes that if local board examining physicians and the specialists attached to medical advisory boards are given an opportunity to attend seminars on the subject it will tend to bring about a desired uniformity in the psychiatric examinations. Those who were invited to attend the conference in Washington, December 5, included Dr. Winfred Overholser, U. S. P. H. S., St. Elizabeth Hospital, Washington, D. C.;

Lieut. Col. William C. Porter, U. S. Army, Walter Reed Hospital, Washington, D. C.; Capt. Dallas G. Sutton, U. S. Navy, Naval Hospital, Washington D. C.; Dr. Howard W. Potter, Bellevue Hospital, New York; Dr. Harry A. Steckel, American Psychiatric Association, Syracuse, N. Y.; Dr. Martin J. Cooley, Veterans Administration, Washington, D. C.; Mr. Frederic Osborne, chief of Civilian Advisory Committee on Selective Service; Dr. Roscoe W. Hall, St. Elizabeth Hospital, Washington, D. C.; Dr. Harry Stack Sullivan, White Psychiatric Foundation, New York; Dr. Wendell S. Muncie, Johns Hopkins Hospital, Baltimore; Dr. Rose Chapman, Sheppard and Enoch Pratt Hospital, Towson, Md., and Lieut. Col. Charles B. Spruit, General Headquarters, Army War College.

STUDY OF AIRPLANE PILOTS

The assistant secretary of commerce, Robert H. Hinckley, has announced the completion of arrangements by which the Mayo Foundation will conduct extensive research into the correlation between physical examinations of civilian airplane pilots and their actual performance in flight. The Mayo Foundation will conduct this research as a public service and at its own expense, the only cost to the government being flight courses for several of the doctors conducting these studies. The aim will be to develop more accurate yardsticks to predict on the ground the relative ability of pilots and prospective pilots. Ten Mayo Foundation specialists in various fields who studied the student pilots on the ground followed them step by step through the flight courses. Several of the Mayo physicians are already flight surgeons and others will take the civilian pilot training courses along with the students who are studying.

CALIFORNIANS SEND SUPPLIES TO BRITISH RED CROSS

The Medical Committee of the British War Relief Association of Northern California has purchased several ambulances and mobile canteens and sent them to the British Red Cross; the committee has been sending also other medical and surgical supplies. A plan is under way now to purchase a desivac machine of 5 liters capacity, which prepares powdered blood plasma in which are all of the original vital blood elements except the erythrocytes and water. Powdered plasma will be sent to the British Red Cross, where the only preparation necessary to make it instantly available for intravenous transfusion will be the addition of sterile distilled water. Desivac machines for yielding powdered plasma are already in use in a few of the military hospitals in England. The committee considers that this machine will be a link also in the medical preparedness program of the United States if powdered plasma becomes necessary for our own military forces; it will also make powdered plasma available to public health departments in the San Francisco Bay area in case of a major industrial disaster.

The unit will be installed if feasible in a San Francisco teaching hospital and all its operations will be under direct supervision of doctors who have volunteered their services.

The machine will be purchased with donations; any one desiring to contribute for this purpose may send donations to the B. W. R. A., Northern California Plasma Fund, 100 Bush Street, San Francisco.

MEDICAL AND SURGICAL SUPPLY COMMITTEE

Nearly $100,000 has been received by the Medical and Surgical Supply Committee of America, 420 Lexington Avenue, New York, in cash and medical supplies and equipment for shipment to emergency hospitals in England. The cash is converted into medical supplies. Among the contributors have been individuals and hospitals in various states and pharmaceutical houses, one of which contributed 1,000,000 vitamin capsules and tablets. The Anglo-American Committee for War Refugees cabled the committee requesting hot water bottles and rubber sheeting, and in response 500 hot water bottles and 1,000 yards of rubber sheeting are being shipped. The committee hopes to send a total of 1,000 first aid outfits and an equal number of operating sets to England before Christmas to help equip air raid shelters, first aid posts and auxiliary hospitals. According to Mrs. Ronald B. Balcom, executive chairman, the administrative expenses of the committee remain at less than 4.5 per cent of the contributions. New names on the National Committee are Drs. Chester D. Allen, William D. Anderson, Daniel H. Anthony, Julian B. Blue, Kinsey M. Buck, Edward G. Campbell, Willis C. Campbell, Arthur F. Cooper, Jewell M. Dorris, all of Memphis, Tenn.; Dr. Claude B. Squires of Charlotte, N. C., and Dr. Julian Deryl Hart of Durham, N. C., Dr. Thomas H. Cheavens of Dallas, Texas, and Dr. Joel J. Pressman of Los Angeles.

COMMITTEE ON NURSING APPOINTED

The Health and Medical Committee of the Council of National Defense announced membership of a subcommittee on nursing, of which Miss Mary Beard, director of nursing, American Red Cross, has been named chairman. Members are Miss Marion Howell, dean of the Frances Payne Bolton School of Nursing, Western Reserve University, Cleveland; Miss Nellie Hawkinson, professor of nursing education, University of Chicago; Sister M. Olivia, dean of the School of Nursing, Catholic University of America, Washington, D. C., and Miss Julia Stimson, chairman of nursing, Council of National Defense, and president of the American Nurses' Association, New York. Functions of the subcommittee on nursing are to conduct investigations and studies of the nursing needs of the nation and make recommendations for coordinating nursing requirements of the country as a whole with those for national defense.

NEW MILITARY HOSPITAL IN SANTA BARBARA

Plans have been announced for a new hospital in Santa Barbara, Calif., to cost approximately $1,042,800 and with a capacity of 750 beds to be built in accordance with war department policy governing provision of such establishments for new stations. Full facilities will be provided for competent operation and administration and include such buildings as surgical, medical and isolation ward buildings, dental and eye, ear, nose and throat clinics, an infirmary for sick call and first aid, a complete laboratory, physical therapy building, administration and surgery buildings, mess halls, quarters for bachelor officers, for nurses and for other medical personnel, recreation buildings, post exchange, workshops and storage buildings, and buildings for the fire protection service. It is expected that the hospital will be ready for occupancy early in 1941.

ARMY RESERVE OFFICERS ORDERED TO ACTIVE DUTY

WAR DEPARTMENT

The following additional medical reserve corps officers had been ordered to extended active duty with the regular army by direction of the War Department, Washington, D. C., up to November 29:

CAMPBELL, Clayton C., Jr., 1st Lieut., Long Beach, Calif.
CAMPBELL, Paul Andrew, Captain, Chicago.
COOPER, Arlin Bernice, 1st Lieut., Ben Wheeler, Texas.
ESTES, Woodrow B., 1st. Lieut., Miami, Fla.
EVANS, Wesley Mort, 1st Lieut., Munhall, Pa.
HEWLETT, Frank Wilson, 1st Lieut., Coral Gables, Fla.
HOLSCHER, Edward Charles, 1st Lieut., Kirkwood, Mo.
JAASTAD, Leonard Binning, 1st Lieut., Milwaukee.
LIPIN, Raymond Joseph, 1st Lieut., Pasadena, Md.
NOVAK, John Goodman, 1st Lieut., Pittsburgh.
RININGER, Harold Casper, Rockport, Ind.
SAWYER, Lester Jacob, 1st Lieut., San Francisco.
SHEAR, Manuel Heine, 1st Lieut., Austin, Texas.
WITTELS, Theodore S., 1st Lieut., Newton, Texas.

SECOND CORPS AREA

The following additional medical reserve corps officers had been ordered to active duty by the Commanding General, Second Corps Area, up to November 29. The Second Corps Area comprises the states of New York, New Jersey and Delaware.

AYER, Guy D., Jr., 1st Lieut., Cooperstown, N. Y.
BASTON, Frank K., 1st Lieut., Tulley, N. Y., 1st Military Area.
BLAUVELT, Willard J., 1st Lieut., Port Byron, N. Y., 1st Military Area.
BLEICHFELD, Samuel, Captain, 119 Highland Avenue, Buffalo, New York, 1st Military Area.
CALEF, Victor C., 1st Lieut., New York.
CARPENTER, Robert B., Captain, Buffalo.
DODGE, Lynn, Major, Fairport, N. Y.
FISHBEIN, Elliot, 1st Lieut., Paterson, N. J.
FREEMAN, Ray McArthur, Captain, Linden, N. J.
GERSHMAN, Maurice, 1st Lieut., Brooklyn, 2d Military Area.
HERO, Bryon A., 1st Lieut., Long Island City, N. Y., 2d Military Area.
KASICH, Milosh, Major, New York.
MARSH, Edward H., Major, 7 Leith Place, White Plains, New York, 2d Military Area.
MAXWELL, Cyrus H., Captain, Albany, N. Y.
MENDELSON, Michael, 1st Lieut., Binghamton, N. Y.
MORAN, John F., Jr., 1st Lieut., Lambertville, N. J.
PASCALE, Vincenzo, Lieut. Col., New York.
RAINEY, Harry G., 1st Lieut., Ogdensburg, N. Y., 1st Military Area.
RAPPOPORT, Milton, 1st Lieut., Brooklyn, 2d Military Area.
SMITH, Percy L., 1st Lieut., Dayton, N. J.
STANSBURY, Frederick C., 1st Lieut., Syracuse, N. Y.
WAUGH, David D., 1st Lieut., Brooklyn, 2d Military Area.
WINTER, Carl M., 1st Lieut., Camden, N. J., 3d Military Area.

THIRD CORPS AREA

Following is a list of additional medical reserve corps officers who up to November 29 had been ordered to extended active duty by Third Corps Area order. The Third Corps Area comprises the states of Pennsylvania, Virginia, District of Columbia and Maryland.

ABRAMOVITZ, Leonard Jerome, 1st Lieut., Baltimore.
BANKERT, Charles William, 1st Lieut., Linesville, Pa.
BASTACKY, Morris, 1st Lieut., Pittsburgh.
BIDUS, Leo Marion, 1st Lieut., Philadelphia.
BISHOP, William Russell, Captain, Flint Hill, Va.
BLUMBERG, Leon David, 1st Lieut., Philadelphia.
CARP, Albert Alexander, 1st Lieut., Philadelphia.
CHERKASKY, Martin, 1st Lieut., Philadelphia.
DEWOODY, Gerald McDowell, Captain, Center, Pa.
DROZD, Joseph, 1st Lieut., Baltimore.
ENGELMAN, Frank Ephraim, Captain, Pittsburgh.
GAEV, Samuel David, Captain, Philadelphia.
GRIFFITHS, John Owen, 1st Lieut., Philadelphia.
HABER, Richard Edward, 1st Lieut., Pittsburgh.
JOHNSON, William Arthur, 1st Lieut., Uniontown, Pa.
KRAUSZ, Martin Richard, 1st Lieut., Philadelphia.
LAWRY, Lee Llewellyn, Jr., 1st Lieut., Philadelphia.
LICHTENSTEIN, George Maurice, 1st Lieut., Philadelphia.
MERLIN, Albert Abraham, 1st Lieut., Philadelphia.
MICHAELSON, Ernest, 1st Lieut., Bladensburg, Md.
SACHS, Fred, 1st Lieut., Bloomsburg, Pa.
SCHWAB, John Edward, 1st Lieut., Philadelphia.
SISSON, Harold Edward, 1st Lieut., Haynesville, Va.
STANLEY, Thomas Zborowski, 1st Lieut., Wilkes-Barre, Pa.
STEINMETZ, Henry Gottlieb, Captain, Arlington, Va.
STRATTON, James David, 1st Lieut., Brackenridge, Pa.
VIOLETTI, Raffaele Lombardo, 1st Lieut., Philadelphia.
VOLKIN, Leonard Bernard, 1st Lieut., Ernest, Pa.
WARREN, Charles Weston, 1st Lieut., Upperville, Va.
WOODHOUSE, Samuel Lawrence, Jr., Captain, Philadelphia.

FOURTH CORPS AREA

The following additional medical reserve officers have been ordered to active duty by Fourth Corps Area Order since November 22. The Fourth Corps Area comprises the states of Tennessee, North Carolina, South Carolina, Alabama, Georgia, Mississippi, Florida and Louisiana.

BELL, John A., Jr., 1st Lieut., Dublin, Ga.
BOWDEN, Ralph O., 1st Lieut., Savannah, Ga.
BRANDON, Robert W., Jr., 1st Lieut., Martin, Tenn.
BUMGARNER, John R., 1st Lieut., Wilkesboro, N. C.
CALDWELL, Gene D., 1st Lieut., Shreveport, La.
CATHELL, Edwin J., 1st Lieut., Lexington, N. C.
CHERRY, James H., 1st Lieut., Asheville, N. C.
CHEW, Nathaniel J., 1st Lieut., Bristol, Tenn.
CROOM, Robert D., Jr., Captain, 1st Lieut., Maxton, N. C.
CROW, Robert H., 1st Lieut., Cowpens, S. C.
DOWMAN, Charles E., 1st Lieut., Atlanta, Ga.
ELDRIDGE, Franklin G., Captain, Valdosta, Ga.
EVANS, Milton L., 1st Lieut., Memphis, Tenn.
FAILLA, Anthony, 1st Lieut., Pineville, La.
FERRELL, Thomas J., 1st Lieut., Waycross, Ga.
FINGER, Elliott, Captain, Marion, S. C.
FREEMAN, James V., 1st Lieut., Jacksonville, Fla.
GALIN, Albert N., 1st Lieut., Brunswick, Ga.
GOLSAN, Willard R., Captain, Macon, Ga.
HAMILTON, Alfred T., 1st Lieut., Chapel Hill, N. C.
HAMMOND, Alfred F., Jr., 1st Lieut., Grifton, N. C.
HARPER, Sage, 1st Lieut., Wray, Ga.
HART, Oliver J., Captain, Winston-Salem, N. C.
HENSON, George G., Captain, Knoxville, Tenn.
HOCHFELDER, Bernard, 1st Lieut., New Orleans.
HOLDER, Franklin P., 1st Lieut., Eastman, Ga.
HOUSER, Frank M., 1st Lieut., Macon, Ga.
HUFSTEDLER, Fred E., 1st Lieut., Lenoir City, Tenn.
HUTCHINS, James D., 1st Lieut., Crystal Springs, Miss.
HYER, Yeadon M., 1st Lieut., Chester, S. C.
JONES, Lewis M., 1st Lieut., Opelika, Ala.
KENDALL, Cyrus E., 1st Lieut., Madison College, Tenn.
LESHER, John H., 1st Lieut., Knoxville, Tenn.
LEWIS, Walter G., 1st Lieut., Stokesdale, N. C.
LYLES, Robin, 1st Lieut., Columbia, Tenn.
MacLENNAN, Edward R., 1st Lieut., Opp, Ala.
MANLEY, David B., 1st Lieut., Holopaw, Fla.
MILLER, James B., 1st Lieut., Columbia, Tenn.
MORROGH, Lailor A., Jr., 1st Lieut., Breaux Bridge, La.
NEVANS, Herman, 1st Lieut., Livingston, Tenn.
PERKINS, George E., 1st Lieut., Lake Worth, Fla.
POMERANCE, Joseph B., Captain, Miami Beach, Fla.
RAINEY, William T., Captain, Tiptonville, Tenn.
SAPPINGTON, Thomas A., 1st Lieut., Thomaston, Ga.
SINCLAIR, Robey T., Jr., 1st Lieut., Whiteville, N. C.
SLIPAKOFF, Leon, 1st Lieut., New Iberia, La.
SLOAN, William S., 1st Lieut., Wilson, N. C.
SMITH, Daniel L., Jr., 1st Lieut., Spartanburg, S. C.
SORRELLS, John E., 1st Lieut., Iowa, La.
STAPLETON, John L., 1st Lieut., Columbus, Ga.
TAYLOR, Harlan H., 1st Lieut., Cookeville, Tenn.
TIMMONS, Thaddeus A., 1st Lieut., Pamplico, S. C.
WALSH, John K., 1st Lieut., Florence, S. C.
WATT, Edward C., Jacksonville, Fla.
WHITFIELD, Robert L., Jr., Captain, Jamestown, Tenn.
WORK, Samuel D., Jr., 1st Lieut., Forsyth, Ga.
YOUNG, Henry D., Jr., 1st Lieut., Bushnell, Fla.

Orders Revoked

Orders have been revoked on the following named officers reported on a previous report:

ARP, Charles R., 1st Lieut., Atlanta, Ga.
BRABHAM, Vance W., Jr., 1st Lieut., Augusta, Ga.
HARRELL, Henry L., Captain, Ocala, Fla.

FIFTH CORPS AREA

The following additional medical reserve corps officers had been ordered by Fifth Corps Area Order to active duty up to November 22. The Fifth Corps Area comprises the states of Ohio, West Virginia, Indiana and Kentucky.

AIR, Clements W., 1st Lieut., Ludlow, Ky.
BATEMAN, Robert G., 1st Lieut., Richmond, Ky.
BLOUNT, Rankin C., 1st Lieut., Lexington, Ky.
BROSHEER, John R., 1st Lieut., Middlesboro, Ky.
COHEN, Robert, Captain, Louisville, Ky.
DITTMER, Jack E., 1st Lieut., Valparaiso, Ind.
FLAX, Moses, 1st Lieut., Paintsville, Ky.
HOLTZCLAW, Morris Richard, 1st Lieut., Somerset, Ky.
LOONEY, John E., 1st Lieut., Praise, Ky.
McALLISTER, Max F., 1st Lieut., Outwood, Ky.
McCOLLUM, Wendell D., 1st Lieut., Beattyville, Ky.
NOE, Joseph T., 1st Lieut., Wheelright, Ky.
PORTER, Robert F., 1st Lieut., Middlesboro, Ky.
STERNBERG, Elmer G., 1st Lieut., Cincinnati.
STINE, Frederick, 1st Lieut., Fort Thomas, Ky.

EIGHTH CORPS AREA

The following additional medical reserve officers had been ordered to active duty by Eighth Corps Area order up to December 6. The Eighth Corps Area comprises the states of Colorado, Arizona, New Mexico, Oklahoma and Texas.

AHERN, William Thomas Aloysius, 1st Lieut., Mesa Verde, Colo.
ALBI, Roger Vincent, 1st Lieut., Denver.
ANGUS, Howard, 1st Lieut., Lawton, Okla.
AUSTIN, Dale J., 1st Lieut., Dallas, Texas.
BERK, Ira Jay, Captain, McAllen, Texas.
BEST, Ralph L., 1st Lieut., Skiatook, Okla.
BLOSS, Claude M., 1st Lieut., Okemah, Okla.
BRALLIAR, John Seward, 1st Lieut., Wickenburg, Ariz.
BURNETT, Thomas Raynes, Major, Mission, Texas.
CARLOCK, John Hoyle, Jr., 1st Lieut., Ardmore, Okla.
CLARK, John Vincent, 1st Lieut., Oklahoma City.
CUNNINGHAM, Charles Donald, 1st Lieut., Seminole, Okla.
DIMOND, Edgar A., 1st Lieut., Muskogee, Okla.
EVANS, Robert Erle, 1st Lieut., Ada, Okla.
EWELL, William C., 1st Lieut., Tulsa, Okla.
FRY, Francis P., Jr., 1st Lieut., Frederick, Okla.
GALLAGHER, C. A., 1st Lieut., Oklahoma City.
GOOCH, James Oliver, 1st Lieut., Shamrock, Texas.
GRANT, Richard B., Jr., Captain, Bryan, Texas.
HANDLEY, James Jefferson, Major, Greenville, Texas.
HARTGRAVES, Thomas Anderson, Major, Phoenix, Ariz.
HAWKER, Laverne Joseph, 1st Lieut., Fort Worth, Texas.
HOLMES, Raynor E., Jr., 1st Lieut., Canon City, Colo.
HOPPER, John Jackson, 1st Lieut., Stanton, Texas.
HUGGINS, James Richard, 1st Lieut., Oklahoma City.
JORDAN, Robbie C., 1st Lieut., Austin, Texas.
KELLAM, Seth White, 1st Lieut., Menard, Texas.
KERNEK, Clyde, 1st Lieut., Holdenville, Okla.
KERNEK, Paul, 1st Lieut., Oklahoma City.
KUYKENDALL, Fred D., 1st Lieut., Eaton, Colo.
LEIGHT, Sidney B., 1st Lieut., Denver.
LEMEE, Raymond Adolphe, 1st Lieut., Odessa, Texas.
LERNER, Ben Leanard, 1st Lieut., Houston, Texas.
LIVINGSTON, Lawrence G., Captain, Cordell, Okla.
McFARLING, James Everett, 1st Lieut., Humble, Texas.
MARTIN, Howard C., 1st Lieut., Oklahoma City.
MINOWITZ, David Louis, 1st Lieut., Fairplay, Colo.
NICKS, Frank Irvin, 1st Lieut., Manitou Springs, Colo.
O'NEILL, Francis Edward, 1st Lieut., Sanderson, Texas.
PEACOCK, George Eugene, 1st Lieut., Jacksonville, Texas.
PHILLIPS, Oliver Mack, 1st Lieut., Fort Worth, Texas.
PICKETT, Britton E., Jr., 1st Lieut., Carrizo Springs, Texas.
PIERSON, Marcus A., 1st Lieut., Galveston, Texas.
RAFTER, John Ralph, 1st Lieut., Muskogee, Okla.
RECORDS, John Williams, 1st Lieut., Oklahoma City.
ROARK, Frank Earl, 1st Lieut., Monticello, Utah.
SANGER, Paul G., 1st Lieut., Vinita, Okla.
SCHUESSLER, Willard W., Captain, Dallas, Texas.
SEYLER, Louis Walter, 1st Lieut., Commerce, Texas.
SIEVER, James Monroe, 1st Lieut., Dallas, Texas.
SIMON, John Franklin, 1st Lieut., Alva, Okla.
STUBBS, James B., 1st Lieut., Sweetwater, Texas.
STUMP, Robert M., Captain, Phoenix, Ariz.
SWANSON, Howard Edward, 1st Lieut., Denver.
SWEARINGEN, Robert Goodwin, Captain, Corpus Christi, Texas.
SWINNY, Boen, Major, San Antonio, Texas.
SWITZER, Fred D., 1st Lieut., Hugo, Okla.
TUBBS, William M., 1st Lieut., Silver City, N. M.
TURNBOW, William Ray, 1st Lieut., Tulsa, Okla.
VAUGHAN, Luther Matthews, 1st Lieut., Houston, Texas.
WAGNER, Gerald W., 1st Lieut., McKinney, Texas.
WILKERSON, John M., 1st Lieut., Checotah, Okla.
WILSON, Jewell R., 1st Lieut., Seminole, Okla.
ZEDLER, Garland Gus, 1st Lieut., Austin, Texas.
ZEHNPFENNIG, Urban H., 1st Lieut., Merkel, Texas.

Orders Revoked

The recent Eighth Corps Area headquarters order assigning the following medical reserve corps officers to active duty have been revoked:

COOPER, Elmer E., 1st Lieut., Nogales, Ariz.
MARTIN, Howard C., 1st Lieut., Oklahoma City.
ROARK, Frank Earl, 1st Lieut., Monticello, Utah.
STOUGH, Austin R., 1st Lieut., McAlester, Okla.
WALLACE, Gordon K., Captain, Dallas, Texas.

NAVAL RESERVE OFFICERS ORDERED TO ACTIVE DUTY

The following additional naval reserve officers have been ordered to active duty:

ASHTON, Wilbur L., Lieut. Comdr., M. C.-V. (S), Umatillo, Fla., Naval Air Station, Jacksonville, Fla.
BENJAMIN, Emanuel W., Lieut. Comdr., M. C.-V. (S), Providence, R. I., Naval Hospital, Newport, R. I.
BOLES, Albert, Lieut. Comdr., M. C.-O., Oakland, Calif., Naval Air Station, Alameda, Calif.
CARTER, Curtis H., Lieut. (j. g.) M. C.-V. (G), Augusta, Ga., Naval Hospital, Pensacola, Fla.
CHAMBERLAIN, John W., Lieut. (j. g.) M. C.-O., Belmont, Mass., Naval Reserve Aviation Base, Squantum, Mass.
FRANCE, Richard, Lieut., M. C.-V. (S), Baltimore, Naval Hospital, Philadelphia.
GEIBEL, Frank B. C., Lieut., M. C.-V. (S), Washington, D. C., Naval Hospital, Philadelphia.
GROVE, Pembroke, T., Lieut. (j. g.) M. C.-V. (S), Washington, D. C., Naval Hospital, San Diego, Calif.
HALBACH, Robert M., Lieut. Comdr., M. C.-V. (S), Jamestown, R. I., Naval Hospital, Newport, R. I.
HANSON, Frederick C., Lieut., M. C.-V. (S), Providence, R. I., Naval Torpedo Station, Newport, R. I.
HORWITZ, Ellis Berry, Lieut. Comdr., M. C.-V. (S), Philadelphia, Naval Hospital, Philadelphia.
HUBER, Paul R., Lieut. Comdr., M. C.-O., Chicago, Ninth Naval District Headquarters, Great Lakes, Ill.
HUGHES, William N., Lieut. Comdr., M. C.-V. (S), Providence, R. I., Naval Hospital, Newport, R. I.
IVORY, Harry S., Lieut. Comdr., M. C.-V. (S), Point Pleasant, N. J., Naval Air Station, Lakehurst, N. J.
KEARNS, Jerry J., Lieut. Comdr., M. C.-V. (S), Chicago, Naval Training Station, Great Lakes, Ill.
LLOYD, Allen S., Lieut., M. C.-V. (S), Los Angeles, Norfolk Naval Hospital, Portsmouth, Va.
LUPTON, Charles H., Lieut. Comdr., M. C.-V. (S), Norfolk, Va., Norfolk Naval Hospital, Portsmouth, Va.
MACALUSO, Anthony, Lieut. Comdr., M. C.-O., Newton, Mass., Naval Reserve Aviation Base, Squantum, Mass.
NORTHINGTON, Page O., Comdr., M. C.-O., New York, Third Naval District Headquarters, New York.
O'CONNOR, Harry A. D., Lieut. Comdr., M. C.-V. (S), New York, Naval Hospital, Brooklyn.
PAGE, Henry F., Lieut. (j. g.) M. C.-V. (S), Philadelphia, Naval Hospital, Philadelphia.
SCARNEY, Herman D., Lieut., M. C.-O., Detroit, Naval Reserve Aviation Base, Detroit (Grosse Isle), Mich.
SCHMIDHOFFER, Ernst, Lieut. (j. g.) M. C.-V. (S), Boston, Naval Hospital, Chelsea, Mass.
SCHNEIDER, Herbert H., Lieut. (j. g.) M. C.-V. (G), Rochester, Minn., Naval Hospital, Pensacola, Fla.
SCHWAB, William John, Lieut. (j. g), M. C.-V. (G), Providence, R. I., Naval Torpedo Station, Newport, R. I.
SMART, Frank P., Lieut. Comdr., M. C.-V. (S), Norfolk, Va., Norfolk Naval Hospital, Portsmouth, Va.
STEINMUELLER, Karl J., Lieut. Comdr., M. C.-V (S), Baltimore, Naval Hospital, Annapolis. Md.
TURNER, Howard K., Lieut. Comdr., M. C.-V. (S), Providence, R. I., Naval Hospital, Newport, R. I.
WEAVER, Harry S., Jr., Lieut., M. C.-O., Philadelphia, Fourth Naval District Headquarters, Philadelphia.
WITTSON, Cecil L., Lieut., M. C.-V. (S), Central Islip, N. Y., Naval Training Station, Newport, R. I.

ORGANIZATION SECTION

ASSOCIATED HEALTH FOUNDATION, INC.

The Associated Health Foundation, Inc., with offices at 57 West Fifty-Seventh Street, New York, has received a license from the State Department of Insurance as provided under the recent amendment to the New York state insurance laws and has been approved by the State Department of Social Welfare. The foundation is not directly connected with or controlled by either the Medical Society of the State of New York or any county medical society. It is a nonprofit, medical expense indemnity plan organized in accordance with the law referred to. It is managed by a nonsalaried board of trustees made up of fifteen physicians and ten laymen. Medical matters are handled by a medical board composed of eight physicians. Any physician licensed in the state of New York is eligible to become a participating member of the plan. Members are permitted free choice of any physician who agrees to the terms of the plan.

The plan is designed to provide adequate medical care for persons below the "comfort level." Annual income limits are from $1,800 for a single person to $3,000 for a family with two or more children. Subscribers' dues are $18 a year for a single person, $30 a year for husband and wife, $12 a year for a dependent child between 16 and 18 years old and $7.50 for a dependent child under 16 years of age. For this the subscriber receives "complete medical and surgical care, including x-ray and laboratory tests from the underwriting physicians." The following classes of cases are excluded: workmen's compensation, elective surgery during the first eleven months, obstetric care during the first ten months, drug addiction, chronic alcoholic conditions, venereal diseases and nervous and mental diseases. Services are also not given to any one who "prior to or at the time of their application for membership" have had any one of the following diseases: insanity, pernicious anemia, cancer, diabetes, psoriasis or any incurable skin disease, tuberculosis, chronic nephritis, osteomyelitis or chronic heart disease, or for any disease or condition existing at the time of the subscriber's application, venereal diseases during the first ten months, and plastic or cosmetic surgery.

The incomes from subscribers are to be divided as follows: 20 per cent for administration, and of the remaining 80 per cent "60 per cent thereof is used to pay general practitioners on a capitation basis and the remaining 40 per cent to pay specialists, consultants, surgeons, x-ray and laboratory men on a unit basis using the schedule of fees payable for services rendered under the workmen's compensation schedule as a basis." This scheme of distribution applied to the $18 annual fee for an individual would give $3.60 for administration, $8.64 for the capitation fee for general practitioners and $5.70 for consultants, x-ray and laboratory service. The amount available per person for physicians on the family rate would be still less. A physician who enters into this agreement can terminate his participation only after giving the corporation notice in writing "and such termination shall not be effective until thirteen months from the date of such notice." There is no deductible clause or limit to the amount of services which may be demanded and given during a contract year. The physician is to be paid, as explained, approximately 48 per cent of the subscriber's premiums regardless of the amount of service the physician gives to the subscriber.

OFFICIAL NOTES

RADIO BROADCASTS

"Doctors at Work" is the title of the sixth annual series of dramatized radio programs being presented by the American Medical Association and the National Broadcasting Company.

The series opened Wednesday, November 13, and will run for thirty consecutive weeks, closing with a broadcast from the A. M. A. meeting at Cleveland on June 3, 1941. The program is scheduled for 10:30 p. m. eastern standard time (9:30 central, 8:30 mountain, 7:30 Pacific time) over the Blue network, other N. B. C. stations and Canadian stations.

These programs are broadcast on what is known in radio as a sustaining basis; that is, the time is furnished gratis by the radio network and local stations and no revenue is derived from the programs. Therefore, local stations may or may not take the programs, at their discretion, except those stations which are owned and operated by the National Broadcasting Company.

Some radio stations may be unable to broadcast the program at the regular scheduled time and may transcribe and broadcast it at another hour or even on another day. It is advisable therefore to verify the time by reference to local newspapers or by telephoning the local Blue network stations.

The programs will dramatize what modern medicine offers the individual in the way of opportunities for better health and the more successful treatment of disease. Incidental to this main theme the programs will explain the characteristics of the different fields of modern medicine and its specialties.

Descriptive posters for local distribution may be had gratis from the Bureau of Health Education, American Medical Association, 535 North Dearborn Street, Chicago. Program titles will be announced weekly in THE JOURNAL and monthly in *Hygeia*, the Health Magazine.

Tickets are available for each broadcast. Address the Bureau of Health Education, American Medical Association, 535 North Dearborn Street, Chicago. Tickets are free, but a stamped self-addressed envelop should accompany requests.

The next three programs to be broadcast, together with their dates and their topics, are as follows:

December 18. A Stitch in Time.
December 25. The Country Doctor.
January 1. Otorhinolaryngologist.

THE CLEVELAND SESSION

Applications for Hotel Reservations

A list of Cleveland hotels together with the rates for rooms may be found on advertising page 36 of this issue of THE JOURNAL. With this list will be found an application form that may be used to secure reservations through the Subcommittee on Hotels of the Local Committee on Arrangements. This application form may be clipped and, when it is properly filled in, should be sent at once to Dr. Edward F. Kieger, Chairman of the Subcommittee on Hotels, Cleveland Convention and Visitors' Bureau, Inc., 1604 Terminal Tower, Cleveland, Ohio.

Those who expect to attend the annual session of the American Medical Association should send in their applications at the earliest possible time. Applicants for reservations are especially requested to include a second and a third choice in order that good accommodations may be assured if the desired reservation cannot be had at the hotel of preference. It will greatly expedite matters if requests for reservations are addressed directly to Dr. Kieger.

Motion Pictures in the Scientific Exhibit

The Committee on Scientific Exhibit announces that motion pictures in the Scientific Exhibit at the Cleveland session will be shown in areas provided for that purpose rather than in exhibit booths. Application blanks for a place on the motion picture program may be obtained from the Director, Scientific Exhibit, American Medical Association, 535 North Dearborn Street, Chicago.

Medical News

(PHYSICIANS WILL CONFER A FAVOR BY SENDING FOR THIS DEPARTMENT ITEMS OF NEWS OF MORE OR LESS GENERAL INTEREST: SUCH AS RELATE TO SOCIETY ACTIVITIES, NEW HOSPITALS, EDUCATION AND PUBLIC HEALTH.)

ALABAMA

Regional Meeting.—The Northeastern Division of the Medical Association of the State of Alabama met at Alexander City, October 10, with the Tallapoosa County Medical Society acting as host. The program included:

Dr. Henry Ernest Askin, Alexander City, Convulsions.
Dr. James R. Garber, Birmingham, Diagnosis in Obstetrics.
Dr. Amos C. Gipson, Gadsden, The Role of Allergy in Pediatric Practice.
Dr. James O. Morgan, Gadsden, Indications for Surgery in Peptic Ulcer.
Dr. George Knox Spearman, Anniston, Perennial Hay Fever.
Dr. James Marvin Washam, Talladega, Appendicitis.

ARKANSAS

District Meetings.—Dr. Augustus A. Street, Vicksburg, Miss., discussed "Duodenal Ulcer" before the Fifth Councilor District Medical Society in Camden, October 10, and Dr. William H. Anderson, Booneville, president of the Mississippi State Medical Association, "A Doctor's Duty to Himself, to His Fellow Men and to the Public."——The Second District Medical Society met in Batesville, October 14. Drs. William T. Pride, Memphis, Tenn., discussed "Some of the Common Difficulties in Obstetrics" and Darmon A. Rhinehart, Little Rock, "X-Ray Treatment for Menorrhagia."——The Third Councilor District Medical Society was addressed in Helena, October 24, by Drs. Robert Lyle Motley, Memphis, Tenn., on "Indication and Uses of Sulfanilamide, Sulfapyridine, Sulfathiazole"; David T. Hyatt, Little Rock, "Vitamin Therapy"; Alan G. Cazort, Little Rock, "Allergic Dermatitis," and William R. Brooksher, Little Rock, "Medical Preparedness." The dinner session was addressed by Dr. Downey L. Harris, St. Louis, on "Rabies."

CALIFORNIA

State Board of Examiners.—Dr. Hugo M. Kersten, Los Angeles, has been appointed a member of the state board of medical examiners, succeeding Dr. William R. Molony Sr., Los Angeles, whose term expired last January. Dr. Charles B. Pinkham, San Francisco, was reappointed.

Annual Registration Due January 1.—Every practitioner of medicine and surgery holding a license to practice in California is required by law to register annually, on or before January 1, with the secretary-treasurer of the board of medical examiners and at that time to pay a fee of $2. Failure to pay the required fee within sixty days after January 1 works a revocation of a license, and thereafter a license may be reissued only after application and the payment of a $10 penalty.

CONNECTICUT

Personal.—Dr. Hazen A. Calhoun Jr., Middletown, has been appointed health officer of Haddam, succeeding Dr. Noah A. Burr.——Dr. William F. Verdi, New Haven, has received the gold medal award of the New Haven Advertising Club for his "outstanding contributions to the community."

Annual Registration Due During January.—Every practitioner of medicine and surgery holding a license to practice in Connecticut is required by law to register during January with the state department of health and at that time to pay a fee of $2. Licentiates who have retired from active practice or who live out of the state must register annually but need not pay a fee. A practitioner failing to register is liable to a fine of not more than $5.

Society News.—The Association of Connecticut Tumor Clinics was addressed in Bridgeport, October 17, among others, by Drs. Berkley M. Parmelee on "Irradiation Therapy for Cancer of the Breast" and William L. Weadon, "Treatment of Local Recurrences and Metastases."——Francis John Worsley Roughton, Ph.D., lecturer on physicochemical aspects of physiology, University of Cambridge, England, lectured at a special meeting of the Yale Medical Society, November 19, in New Haven, on "Recent Work on the Chemistry and Functions of Carbonic Anhydrase."

DISTRICT OF COLUMBIA

Changes in Faculty.—Dr. Edward J. Cummings, associate professor of clinical ophthalmology, has been promoted to professor at Georgetown University School of Medicine, Washington, newspapers announce. Other promotions include Dr. William McC. Ballinger to associate professor of gastroenterology and Dr. Edgar W. Davis to professor of clinical surgery.

Course in Aviation Medicine.—The second annual postgraduate course in aviation medicine, including aviation ophthalmology, for graduates in medicine will be held at George Washington University School of Medicine, Washington, D. C., February 3-7. Nineteen guests will lecture on the following subjects, among others:

Physiologic Problems Incident to Flying.
Motility of the Eye.
Color Vision and Night Blindness.
Stereopsis and Depth Perception.
Fundus of the Eye.
Refraction.
Aniseikonia as It Relates to Aviation.
Otolaryngology in Relation to Aviation.
Effect of Altitude in Relation to Military Flying.
Interpretations of Neurologic Signs in Aviation.
Methods of Administration of Oxygen During Flights at High Altitudes.

FLORIDA

Annual Registration Due January 1.—Every practitioner of medicine and surgery holding a license to practice in Florida is required by law to register annually, on or before January 1, with the secretary of the state board of health and at that time to pay a fee of $1. A licentiate failing to register annually is liable to a fine of not more than $50.

GEORGIA

Dr. Lahey to Give Memorial Lecture.—Dr. Frank H. Lahey, Boston, President-Elect of the American Medical Association, will deliver the second Floyd Wilcox McRae Memorial Lecture, December 16, before the Fulton County Medical Society, Atlanta. His subject will be "The Management of Gastric, Duodenal and Jejunal Lesions."

University News.—A sum of $100,000 has been presented to the University of Georgia by S. Price Gilbert, former associate justice of the Georgia supreme court, to construct an infirmary building. According to the New York *Times*, the infirmary will be named in honor of Justice Gilbert's father, the late Dr. Jasper Newton Gilbert, who served with the medical corps of the Confederate Army in the Civil War and later was a country doctor in Georgia. Dr. Gilbert, who lived in Columbus, was graduated at the Medical College of Georgia, Augusta, in 1855.

ILLINOIS

Research Fellowships in Medicine and Dentistry.—The Graduate School of the University of Illinois has established four research fellowships to be awarded for one year in the fields of medicine and dentistry in Chicago at a stipend of $1,200 a year (calendar year with one month's vacation). Fellows are eligible for reappointment in competition with the new applicants. Candidates for these fellowships must have completed a training of not less than eight years beyond high school graduation. This training may have been acquired in any one of the following ways, or the equivalent thereof:

1. Work leading to the B.S. and M.D. degrees (in some instances the candidates would have the M.D. degree, or an additional year or two of hospital training beyond the intern year).
2. Work leading to the B.S., M.S. and D.D.S. degrees.
3. Work leading to the B.S. or B.A. degree in a four year collegiate course and to the D.D.S. degree.
4. Work leading to the B.S., D.D.S. and M.D. degrees.

Candidates should indicate the field of research in which they are interested and submit complete transcripts of their scholastic credits, together with the names of three former science teachers as references. March 1 is the deadline for acceptance of applications. Announcement of the fellowship awards will be made April 1, becoming effective September 1. Formal application blanks may be secured from the Secretary of the Committee on Graduate Work in Medicine and Dentistry, 1853 West Polk Street, Chicago.

IOWA

Society News.—The Des Moines Academy of Medicine and the Polk County Medical Society was addressed, November 20, by Drs. James Barrett Brown, St. Louis, on "Traumatic Surgery" and Andrew C. Ivy, Chicago, "Relation of Physiology to Modern Medicine."

Personal.—Dr. Eric P. Pfeiffer, formerly of Oakville, has been appointed director of the vital statistics division of the state department of health, effective October 1.——Dr. Lester A. Royal, West Liberty, has been named governor of district 132 of Rotary International.

The Rockwood Lecture.—Dr. Isaac Starr, Milton Bixler Hartzell research professor of therapeutics, University of Pennsylvania School of Medicine, Philadelphia, gave the fourth annual Paul Reed Rockwood Lecture of the State University of Iowa College of Medicine in Iowa City, November 13. His subject was "The Ballistocardiogram; Its Contribution to Our Knowledge of the Commoner Diseases Affecting the Heart and Circulation."

LOUISIANA

Annual Renewal Due January 1.—Every practitioner of medicine and surgery holding a certificate to practice in Louisiana is required by law to have his certificate renewed annually, on or before January 1, by the secretary-treasurer of the state board of medical examiners and at that time to pay a fee of $2. The board may by unanimous vote revoke any certificate not renewed.

Society News.—The meeting of the Louisiana Association of Pathologists, November 25, in New Orleans, was opened with an address by Dr. Edwin H. Lawson. Other speakers were Drs. Bjarne Pearson on "Carcinoma of the Cervix Uteri, Its Effect on the Urinary Tract"; Albert E. Casey, "Mitosis Counts in Neoplasia," and Joseph B. Pasternack, "Methods for Rapid Preparation of Paraffin Sections."——Among other speakers, Arthur O. Kastler, Ph.D., Drs. Samuel B. Nadler and Michael E. DeBakey presented a symposium on the recent advances in vitamins before the Orleans Parish Medical Society, November 11. A special scientific session was held with the U. S. Marine Hospital staff, November 22. Dr. John A. Trautman talked on "Sulfonamides in the Treatment of Gonorrhea in the Male" and Dr. William L. Smith presented a case report on a typhoid carrier.

MINNESOTA

Annual Registration Due During January.—Every practitioner of medicine and surgery holding a license to practice in Minnesota is required by law to register annually during January with the secretary of the board of medical examiners and at that time to pay a fee of $2. A licentiate who practices without renewing his license is guilty of a misdemeanor and is liable to prosecution.

Tuberculosis Survey.—The Minnesota State Medical Association has selected Meeker County as the first county in which a statewide campaign to free Minnesota from tuberculosis will be launched. The plan calls for extending to adults through family groups the same preventive service now given to children in the public schools, using the Mantoux test. The project will be under the direction of the committee on tuberculosis of the state medical association, of which Dr. J. Arthur Myers, Minneapolis, is chairman. Cooperating agencies include the Minnesota Public Health Association, the bureau of tuberculosis of the state division of social welfare, the Meeker-Kandiyohi-Swift Counties Medical Society, the Meeker County Christmas Seal Committee and the state department of health.

Society News.—The Ramsey County Medical Society was addressed, November 25, by Drs. Emmett V. Kenefick, St. Paul, on "Leukemias and Leukemoid Reactions"; Alexander E. Brown, Rochester, "Recent Advances in Therapy by Sulfanilamide and Its Related Compounds," and Gordon R. Kamman, St. Paul, "The Rorschach Test as a Method of Personality Analysis."——The general staff of the Mayo Clinic met with the Olmsted-Houston-Fillmore-Dodge Counties Medical Society, November 6; the program was devoted to a symposium on first aid by the physician casually present at an accident. The speakers were Drs. John S. Lundy, John W. Pender, Edward B. Tuohy, Alfred W. Adson, Robert D. Mussey, Gordon B. New and Albert J. Lobb, LL.B., all of Rochester.

MISSOURI

Pilgrimage to Beaumont's Grave.—The annual birthday pilgrimage to William Beaumont's grave, sponsored by the St. Louis Medical Society, was held November 21. Alphonse M. Schwitalla, S.J., made the principal address; Mayor Bernard F. Dickmann placed a wreath on the grave for the city of St. Louis; Dr. Cyrus E. Burford, president of the state medical association, also placed a wreath, and Dr. Herbert S. Langsdorf as president represented the St. Louis City Medical Society.

NEW JERSEY

Interim Meeting of House of Delegates.—The first ad interim meeting of the house of delegates of the Medical Society of New Jersey was held in Newark, November 28. The following progress reports were presented: medical service administration, by Dr. Elton W. Lance, Rahway, president of the board of governors; medical preparedness committee, by Dr. Charles H. Schlichter, Elizabeth, chairman, and hospital relationships committee survey of outpatients, by Dr. Henry B. Decker, Camden, chairman. Dr. Harry R. North, Trenton, discussed a proposal to purchase a permanent home for the state society.

NEW YORK

New Tumor Clinic.—A tumor clinic has been organized at the Saratoga Hospital, Saratoga Springs, according to an announcement by the division of cancer control of the state department of health. Dr. Richard D. Bullard, Saratoga Springs, is executive officer of the new clinic, which is the thirty-sixth in the state, operated as a means of meeting the problem of cancer control in the state.

Annual Registration Due January 1.—Every practitioner of medicine and surgery in New York is required by law to apply annually, on or before January 1, to the secretary of the board of medical examiners for a certificate of registration, on application forms furnished by him, and to pay at that time a fee of $2. The law authorizes the secretary of the board to permit secretaries of duly incorporated medical societies to act as his representatives to receive and transmit to him such applications and fees. Practitioners are liable to severe penalties for failing to register and for continuing in practice thereafter.

New York City

Third Harvey Lecture.—A. Baird Hastings, Ph.D., Hamilton Kuhn professor and head of the department of biological chemistry, Harvard Medical School, Boston, will deliver the third Harvey Lecture of the current season at the New York Academy of Medicine, December 19. His subject will be "The Electrolytes of Tissues and Body Fluids."

Symposium on Chemotherapy.—The Long Island College of Medicine presented a symposium on chemotherapy, November 13. Arnold H. Eggerth, Ph.D., associate professor of bacteriology, opened the program with a historical introduction and other speakers were:

George W. Raiziss, Ph.D., Philadelphia, Mode of Action of the Sulfonamides.
Dr. Elliston Farrell, assistant clinical professor of medicine at Long Island College, Toxic Reactions.
Dr. Charles B. Jones, instructor in surgery, Long Island, The Sulfonamides in Surgery.
Dr. Yale Kneeland Jr., assistant professor of medicine, Columbia University College of Physicians and Surgeons, The Sulfonamides in Pneumonia.
Dr. Alfred Cohn, New York City Department of Health, The Sulfonamides in Gonococcal Infections.
Dr. Josephine B. Neal, clinical professor of neurology, Columbia, The Sulfonamides in Meningitis.
Dr. Lewis A. Koch, clinical professor of pediatrics, Long Island, The Sulfonamides in Pediatric Practice.

NORTH DAKOTA

Personal.—Dr. Bertha B. Brainard, Jamestown, was recently appointed in charge of the student health service at Oregon State College, Corvallis.——Dr. Elvin L. Sederlin, formerly of Laramie, Wyo., has been appointed health officer of Fargo, to succeed Dr. Harvey J. Skarshaug, resigned.

Annual Registration Due January 1.—Every practitioner of medicine and surgery holding a license to practice in North Dakota is required by law to register annually, on or before January 1, with the secretary-treasurer of the board of medical examiners and at that time to pay a fee of $5 if a resident of North Dakota, or $2 if a nonresident. A practitioner may not lawfully practice if he has not registered. If he does so his license may be revoked and can be reinstated on the payment of unpaid fees and $0.50 for each month of default.

OHIO

Dr. Hudson Goes to France.—Dr. Noel Paul Hudson, professor of bacteriology at Ohio State University College of Medicine, Columbus, has been granted a year's leave of absence to join a health commission of the Rockefeller Foundation to work in France. With other members of the commission Dr. Hudson was to leave late in October. He had previously served with the International Health Division of the Rockefeller Foundation. During the World War he served in France as a lieutenant in the Sanitary Corps of the Medical Department, U. S. Army.

Postgraduate Course in Toledo.—The Academy of Medicine of Toledo and Lucas County presented its annual postgraduate course of lectures, December 11-13, with Dr. Andrew C. Ivy, Nathan Smith Davis professor of physiology and professor of pharmacology, Northwestern University Medical School, Chicago, as the lecturer. Dr. Ivy's subjects included: physiologic changes in pregnancy, physiology of labor, the liver and biliary tract, water balance in health and disease, advances in diagnosis and therapeutic interest in the alimentary tract, hypertension, effects of various drugs on peripheral circulation, and heart failure.

PENNSYLVANIA

Annual Registration Due January 1.—Every practitioner of medicine and surgery holding a license to practice in Pennsylvania is required by law to register annually, on or before January 1, with the board of medical education and licensure in the department of public instruction and to pay a fee of $1 or such fee as may be fixed by the department of public instruction. A practitioner who fails to register and who continues to practice is liable to a fine of from $10 to $100.

Special School to Extend Research.—The assets of the Devereux Schools, Devon, have been transferred to the Devereux Foundation, recently established by the founder of the schools, Helena T. Devereux. The foundation will continue to operate the schools and will increase the activities to include research, the further study and treatment of children through psychiatry and psychology and the establishment of scholarships. The schools have ten units and care for more than 200 children. The foundation will be under the direction of a board of trustees including Drs. Louis R. Kaufman, New York; Fred C. Aldridge, Wayne; Gabriel Henry Katz and Edward M. Westburgh, Ph.D., of the Institute of the Pennsylvania Hospital, Philadelphia.

Philadelphia

Women's Cancer Forum.—The annual cancer forum presented to the public by the Women's Auxiliary to the Lankenau Hospital Research Institute, assisted by District No. 1 of the Pennsylvania State Nurses' Association, was held November 25-26 at the Bellevue-Stratford Hotel. Among the speakers were:

Dr. Eugene P. Pendergrass, The Cyclotron—Newest Instrument to Study Cancer and Other Medical Problems.
Otto C. Glaser, Ph.D., Amherst College, Amherst, Mass., The Relation of Biology and the Growth Problem to Cancer.
Dr. Catharine Macfarlane, Further Report on the Reexamination of One Thousand Volunteers.
Dr. Nathaniel Volney Ludwick, The Leukemias.
Dr. Temple S. Fay, Further Observations on Refrigeration in Cancer.

Society News.—Drs. Frederick A. Bothe and Richard H. Meade Jr. addressed the Philadelphia Academy of Surgery, November 4, on "Mesenteric Adenitis" and "Healing of Abdominal Wounds in Perforated Peptic Ulcers" respectively.——Drs. Gabriel Tucker and Ernest A. Spiegel, among others, addressed the Philadelphia Laryngological Society, November 5, on "Hoarseness, Its Mechanism, Clinical Significance, Clinical Signs and Treatment" and "Reaction of the Labyrinth to Rhythmically Interrupted Currents" respectively.——Dr. John F. Fulton, New Haven, Conn., delivered the eighth S. Weir Mitchell Oration before the College of Physicians of Philadelphia, November 6, on "Neurology and War."——Speakers before the Obstetrical Society of Philadelphia, November 7, were Drs. Charles Mazer and Elkin Ravetz on "Effect of Combined Administration of Chorionic Gonadotropin and the Pituitary Synergist on the Human Ovaries," and Clifford B. Lull, "Pubertis Praecox Due to Ovarian Tumor."

RHODE ISLAND

Society News.—Dr. Shields Warren, Boston, addressed the Providence Medical Association, December 2, on "Medicolegal Aspects of Malignant Diseases."——Dr. John F. Kenney will address the Pawtucket Medical Association, December 19, on electrocardiography.

Personal.—Dr. Hilary J. Connor, Providence, has been appointed director of a new department for venereal disease control in the state health department.——Dr. Halsey DeWolf, Providence, has been appointed to the advisory state council of defense to coordinate state defense activities with those of the federal government and Dr. Albert H. Jackvony, Providence, has been made a member of the state selective service appeal board.

TEXAS

Annual Registration Due January 1.—Every practitioner of medicine and surgery holding a license to practice in Texas is required by law to register annually, on or before January 1, with the state board of medical examiners and at that time to pay a fee of $2. If a practitioner fails to renew his registration within sixty days after January 1, his license is suspended.

VIRGINIA

Mental Hygiene Meeting.—Dr. David C. Wilson, Charlottesville, was elected president of the Mental Hygiene Society of Virginia at the annual meeting in Richmond, October 31. Guest speakers at the meeting were Drs. Frank J. Curran, New York, and Joseph E. Barrett, clinical director of Southwestern State Hospital, Marion, who discussed problems of the adolescent and Lawrence Kolb, U. S. Public Health Service, treatment and research in the field of mental disease.

Hospital Changes.—Dr. Grover C. Godwin, Sanatorium, N. C., has been named director of the Roanoke City Tubercular Sanatorium to succeed Dr. John E. K. Flannagan, resigned.——Dr. Samuel E. Hughes, medical director of the Hilltop Sanatorium, Danville, for many years, has resigned, it is reported.——Dr. Willard L. Quennell, has been appointed medical director of the Norfolk General Hospital to succeed Dr. Arthur H. Perkins, resigned.

GENERAL

Meeting of Insurance Physicians.—Dr. Donald B. Cragin, Hartford, Conn., was elected president of the Association of Life Insurance Medical Directors at the annual meeting in Boston, October 16-18. Dr. David E. W. Wenstrand, Milwaukee, became first vice president and Dr. William Bolt, New York, second vice president. Dr. Edwin G. Dewis, Newark, N. J., remains as secretary. Speakers, all of Boston, included Drs. Maurice B. Strauss, on "Disorders Due to Nutritional Deficiency"; Chester S. Keefer, "The Present Status of Chemotherapy in the Treatment of Infectious Diseases," and Merrill Moore, "Alcohol, a Medical Problem."

Southern Psychiatric Meeting.—Dr. Whitman C. McConnell, St. Petersburg, Fla., was named president-elect of the Southern Psychiatric Association at its annual meeting in Jacksonville, Fla., October 21-22, and Dr. Arthur J. Schwenkenberg, Dallas, Texas, was installed as president. Dr. James K. Hall, Richmond, Va., was elected vice president and Dr. Newdigate M. Owensby, Atlanta, Ga., reelected secretary. The 1941 convention will be in Nashville. Among speakers at the meeting were:

Dr. Henry Mason Smith, Tampa, Fla., The Psychological and Economic Influence of Alcohol.
Dr. Gilbert Christian Anderson, New Orleans, The Dental and Oral Basis of Certain Neuropsychiatric States.
Dr. Francis J. Tartaglino, Washington, D. C., Psychotic Reactions Following Sulfanilamide Administration.
Dr. Louis Michael Foltz, Lakeland, Ky., Involutional Melancholia and Its Connection to Gonadotropic Hormone Stimulation.
Dr. Owensby, Homosexuality Corrected by the Pharmacologic Shock Method.

Neuropsychiatric Meeting in Milwaukee.—The Central Neuropsychiatric Association held its nineteenth annual meeting at the Hotel Pfister, Milwaukee, October 25-26, under the presidency of Dr. Percival Bailey, Chicago. Among the speakers were:

Dr. Otto H. Foerster, Milwaukee, Self-Inflicted Lesions of the Skin.
Dr. Max J. Fox, Milwaukee, Treatment of Bulbar and Upper Cervical Types of Poliomyelitis by Perivascular Drainage.
Dr. Theodore L. Squier, Milwaukee, Emotional Factors in Allergic States.
Dr. Andrew I. Rosenberger, Milwaukee, Observations on Treatment of Amyotrophic Lateral Sclerosis (Leukopoliomyelopathy) with Vitamin E.

A symposium on shock therapy was presented by Drs. Lloyd H. Ziegler, James A. Alston, Carroll W. Osgood, Michael Kasak, Harold T. Schroeder, Wauwatosa, and Jack L. Kinsey, Milwaukee. Officers elected were Drs. Louis J. Karnosh, Cleveland, president; Mabel G. Masten, Madison, Wis., vice president, and William C. Menninger, Topeka, Kan., secretary, reelected. The 1941 meeting will be in Detroit and Ann Arbor, Mich.

Influenza Epidemic.—An epidemic of mild influenza has been prevalent in California, reaching its peak during the first week of December. A total of 1,800 cases was reported for December 7, according to the newspapers. Thousands of persons have been stricken since the outbreak began in November. On December 5 the epidemic was said to have spread into

Arizona, Oregon, Washington and Idaho. In Los Angeles several deaths were reported among influenza patients, but there was no indication that the cause of death was the "mild" influenza with which the majority of the stricken were afflicted, according to the New York *Times*. Various schools were closed in the affected areas, including thirteen in San Mateo County, Calif., alone. Of the 21,000 soldiers at Fort Lewis and Camp Murray in Washington, 1,900 were ill. One third of the population in Klamath Falls, Ore., was said to be affected December 8. It is believed that the disease was brought in from Hawaii, where an outbreak had been prevalent since September. The War Department, in answer to inquiries, issued a statement, December 6, that the outbreak in no way resembled that of 1917-1918 and that recovery was rapid.

Symposium on Malaria.—Section N (Medical Sciences) of the American Association for the Advancement of Science, in cooperation with the American Society of Parasitologists, American Society of Tropical Medicine and the National Malaria Committee, will present a symposium on malaria in Philadelphia, December 30-January 1. Among thirty-nine papers to be read will be:

Ernest Carroll Faust, Ph.D., New Orleans, Distribution of Malaria in North America, Mexico, Central America and the West Indies.
Lieut.-Col. James S. Simmons, Office of the Surgeon General, U. S. Army, Washington, D. C., Vectors (Experimental and Natural Infection; Epidemiological Evidence).
Dr. Lewis W. Hackett, Rockefeller Foundation, Buenos Aires, Argentina, Epidemicity and Endemicity of Malaria.
Dr. Henry E. Meleney, Nashville, Tenn., Physiologic Effect of Infection on the Human Organism.
Dr. Erwin E. Nelson, New Orleans, Cinchona Derivatives as Therapeutic Agents in Malaria.
Dr. Herbert C. Clark, Gorgas Memorial Institute, Ancon, C. Z., Prophylaxis in Malaria.
E. Harold Hinman, Ph.D., Tennessee Valley Authority, Wilson Dam, Ala., Management of Water in Controlling Larval Mosquitoes.
Dr. Louis L. Williams Jr., National Institute of Health, Bethesda, Md., An Antimalaria Program for Official Health Agencies.

Clinical and Climatological Society.—Dr. James J. Waring, Denver, was elected president of the American Clinical and Climatological Association at the annual meeting in White Sulphur Springs, W. Va., October 28-30. Drs. Benjamin M. Baker Jr., Baltimore, and Frank A. Evans, Pittsburgh, were elected vice presidents. The program included the following papers:

Drs. Paul D. White and Edward F. Bland, Boston, Coronary Thrombosis—Ten Years Later.
Drs. Robert L. Levy and Richmond L. Moore, New York, Relief of Anginal Pain by Paravertebral Alcohol Block: A Summary of Ten Years' Experience.
Drs. F. Janney Smith and Joseph H. Delaney, Detroit, Kidney Complications of the Chemotherapy of Pneumonia.
Dr. Frederic M. Hanes, Durham, N. C., The Therapy of Deficiency States.
Drs. Charles W. Mills and O. Jocevious Farness, Tucson, Coccidioides Immitis Infection in Southern Arizona.
Dr. Edward N. Packard, Saranac Lake, N. Y., Is Climate Important in the Treatment of Pulmonary Tuberculosis?
Drs. Truman G. Schnabel and Ferdinand Fetter, Philadelphia, Fever Therapy in Rheumatoid Arthritis.

Dr. Rollin T. Woodyatt, Chicago, delivered the Gordon Wilson Lecture under the title "On the Theory of Diabetes."

Hearings on Migration of Indigents.—Views of interested officials, groups and individuals on the problem of 4,000,000 or more destitute persons who migrate annually from state to state were sought in a hearing before the Tolan committee of the House of Representatives in Washington, D. C., November 30 to December 10. The committee was to draft recommendations to be presented to the new Congress in January. Among other phases of the problem discussed were agricultural problems as they affect migration, transient labor, state settlement laws, proposals for federal aid to education, health, housing and public assistance needs of the migrants, the relation of national defense to the interstate migration and economic retardation and its effect on future migrations. Those invited to appear before the committee included Dr. Thomas Parran, surgeon general, U. S. Public Health Service; Dr. George C. Ruhland, health officer of the District of Columbia; Secretary of Labor Frances Perkins; Secretary of Agriculture Claude R. Wickard; Prof. Paul S. Taylor, department of economics, University of California; William H. Stauffer, commissioner of the Virginia Department of Public Welfare; Charles A. Beard, New Milford, Conn., economist, and Frank P. Graham, president of the University of North Carolina, Chapel Hill. Congressman John H. Tolan of California is chairman of the committee.

Conference on Stomach Cancer.—The National Advisory Cancer Council sponsored a two day conference on cancer of the stomach, October 11-12, said to be the first of its kind in America. A discussion of cancer statistics and the hereditary and occupational aspects of gastric cancer was given by Selwyn D. Collins, Ph.D., principal statistician, National Institute of Health; Clarence C. Little, D.Sc., Bar Harbor, Maine, director, Roscoe B. Jackson Memorial Laboratory, and Dr. Madge Thurlow Macklin of the University of Western Ontario Medical School, London. The importance of early diagnosis of cancer of the stomach and the various means of making these tests were discussed by Drs. Rudolf Schindler, Chicago; James Ewing and Gordon P. McNeer, New York, and Max M. Zinninger, Cincinnati. Drs. Alexander Brunschwig and Andrew C. Ivy, Chicago, talked on the physiology and biochemistry of the stomach, and Dr. Harold L. Stewart, Egon Lorenz, Ph.D., and Murray J. Shear, Ph.D., all of Bethesda, Md., and William V. Gardner, Ph.D., New Haven, Conn., on the experimental production of cancer of the stomach in test animals. Other speakers included:

Dr. Cornelius P. Rhoads, New York, Anemia and Deficiency Diseases in Relation to Cancer of the Stomach.
Dr. Mont R. Reid, Cincinnati, How Cancer Clinic Material Can Be Used for Investigations.
Carl Voegtlin, Ph.D., chief, National Cancer Institute, Proposed Program for Study of Cancer of the Stomach.

Others participating included Drs. Leon Schiff, Cincinnati; John J. Morton Jr., Rochester, N. Y.; Alphonse R. Dochez, New York; Walter C. Alvarez, Rochester, Minn.; Shields Warren, Boston, and Milton C. Winternitz and Ashley W. Oughterson, New Haven.

Aviation Award to Three Physicians.—The Collier Trophy, one of the most important national awards in aviation, will be presented during December to Dr. Harry G. Armstrong, captain, U. S. Army Medical Corps, and to Dr. William Randolph Lovelace 2d and Dr. Walter M. Boothby, both of the Mayo Clinic, Rochester, Minn., for research in aviation medicine. The presentation will be made by President Roosevelt on behalf of the National Aeronautic Association. According to an announcement, the trophy for 1939 went "to the airlines of the United States for their outstanding record for safety in air travel during 1939" and to the physicians for "their contribution to this safety record by their work in the field of aviation medicine generally and pilot fatigue in particular." The Collier Trophy is awarded annually for the greatest achievement in aviation in America, the value of which has been demonstrated by actual use during the preceding year. It was first donated in 1911 by Robert J. Collier, then publisher of *Collier's* magazine, and is under the trusteeship of the National Aeronautic Association, which each year designates the committee of awards. Mr. Collier was said to have had the first privately owned airplane in the United States. *Collier's* magazine has supplied a fund for the maintenance of the award, paying for the plaque which accompanies the presentation. The plaque is kept by the winner of the prize, but the trophy is retained only for the year of the award. The recent research dealt with the condition of a person's brain, nerves, blood and reflexes on ascent into the stratosphere. According to the New York *Times*, the three physicians give most of the credit to the pilots of Northwest Airlines, who took part in extensive tests in the Mayo Clinic's low pressure chamber; to D. W. Domlinson, research pilot of Transcontinental and Western Airlines; to several hundred Rochester high school boys who did "fatigue" tests on the Mayo Clinic treadmill; to the men of the Army Air Corps who made standardization of pressure reactions possible, and particularly to a young private named Raymond Whitney, of the matériel division at Wright Field, Dayton, Ohio, who volunteered for the duty of "determining the limits of human tolerance in flight." Week after week Mr. Whitney went into the low pressure chambers where the pressure was dropped to the equivalent of 30,000 feet or more of altitude, went up at the rate of two miles a minute and dropped at the equivalent of power dives of six miles a minute. He received the Distinguished Flying Cross for his work as "an experimental subject in carrying out medical research studies for high altitude flight involving a degree of personal risk well beyond the normal call of duty." Credit also went to Arthur H. Bulbulian, D.D.S., of the Mayo Clinic, for his work in developing the mask which the investigators used in their research.

CORRECTION

Roentgenologic Technicians Instead of Roentgenologists.—In the current comment in THE JOURNAL (November 16, p. 1724) appears a statement beginning "The technical branches associated with medical care include physical therapists, roentgenologists, clinical pathology technicians, lay anesthetists, . . ." In this item the word "roentgenologists" should have been "roentgenologic technicians."

Foreign Letters

LONDON

(From Our Regular Correspondent)

Oct. 26, 1940 (delayed).

The Centenary of the British Medical Journal

Britons have been informed that the bombing of our cities and, at times, even villages is not due to any wish to destroy life and property but is really humanitarian, a means of bringing about a revolution and so ending the war! But, as foreign visitors confirm, all our activities continue with remarkable normality and calmness, though of course the war has altered some of our routine. The medical journals are a little shorter, because of the need to economize paper, but, excepting two local ones, they appear with their usual regularity. The *British Medical Journal* has not allowed the war to interfere with the celebration of its centenary. It publishes a reproduction of the "Introductory Address" of the first number (Oct. 3, 1840) of the *Provincial Medical and Surgical Journal,* which was its direct ancestor. The sentiments of the address are admirable and in no way out of date, but they are expressed with a verbosity which is now obsolete. In January 1857 the title *British Medical Journal* was adopted. The high standard, scientific and practical, always maintained by able editors and eminent contributors, is well known. In an editorial it is stated that this second year of the war finds Britain "an embattled country subject to perpetual air alarms and threatened with invasion, and the treatment of civilian air casualties is a matter of daily concern to doctors throughout the land. The future is obscure; but British hearts are stout." Many messages of congratulation from eminent members of the profession, from the editors of other journals published in the commonwealth and from the Editor of THE JOURNAL A. M. A. are published.

American and Canadian Physicians to Be Licensed for the Duration of the War

The government has made an order under the Emergency Powers Act, passed for the purposes of the war, enabling the General Medical Council to register for the period of the emergency Canadian and United States physicians. They will thus be able to join the Emergency Medical Service with the same privileges as British physicians. Previously we have never had medical reciprocity with the United States and only partial reciprocity with Canada, owing to difficulties which arose from the medical autonomy of the Canadian provinces. Applicants for the new registration must be British subjects or citizens of the United States, be of good character, and must hold some medical diploma recognized for the time being for the purposes of this order by the British General Medical Council as furnishing a guaranty of sufficient knowledge and skill for the efficient practice of medicine, surgery and midwifery.

Science and the War

In order to insure the fullest cooperation of scientific workers with the government in the national war effort a scientific advisory committee has been appointed after discussion with the Royal Society. The committee consists of the following, among whom medical science is represented: Sir William Bragg, president of the Royal Society; E. V. Appleton, F.R.S. (physicist), secretary of the Department of Scientific and Industrial Research; Sir Edward Mellanby, F.R.S. (physiologist), secretary of the Medical Research Council; Sir Edwin Butler, F.R.S., secretary of the Agricultural Council; Prof. A. V. Hill (physiologist), physical secretary of the Royal Society; Prof. A. G. Egerton, F.R.S., biologic secretary of the Royal Society.

The terms of reference of the committee are (1) to advise on any scientific problem referred to them, (2) to advise government departments on the selection of persons for particular lines of scientific inquiry or membership of committees on which scientists are required and (3) to bring to notice promising new scientific or technical developments which may be important in our war effort.

A Bombed Hospital

The following is an example of what hospitals have to go through: A bomb fell on an emergency hospital in southeastern England, killing some patients who had been evacuated from bombed London hospitals. The bomb crashed through three wards, and many patients were buried amid tons of wreckage. The fire department freed some of them, and while the bombers were still overhead the nurses worked among the débris, bringing matresses and administering morphine to trapped patients.

The Feeding of the Army

The Select Committee on National Expenditure has received a report from its subcommittee on army services recommending the greater use of canned foods. Evidence was received indicating the advantages of providing the army with more fruits and vegetables. The subcommittee considers that during the winter a position of extreme complexity and difficulty may arise, owing to the fact that numbers of troops will have to be accommodated in billets and hutments and that efficient catering will play a conspicuous role in maintaining the physical condition and morale of the troops. Canned and prepared foods would give increased variety and in many cases supply the troops with food that merely requires heating, for which skilled cooks would not be required.

A Second Contingent of the American Hospital Unit

The second contingent of the American Hospital Unit, financed by the Allied Relief Fund, has arrived. The vessel in which it came encountered a violent Atlantic storm and as there was no ship's doctor the unit attended the casualties caused among the passengers and crew. The party consists of a surgeon and a physician who are brothers, a radiographer, four nurses and a laboratory technician. There is Dr. Henry Heyl, a 34 year old neurosurgeon, who has trained for eight years under Dr. Jason Mixter and Dr. Gilbert Horrax, leading neurosurgeons. His brother Dr. James Heyl specializes in internal medicine and research work. The radiographer, Mr. William Wykoff, was in Finland during the Russian invasion. He and one of the nurses made their way back to America through Germany and Lisbon.

Marriages

WILLIAM PROVINCE MCGUIRE, Winchester, Va., to Miss Dorothy Elizabeth Robinson of Glen Rock, N. J., at Ridgewood, N. J., October 19.

JOHN THORNTON MITCHELL, Miami, Fla., to Miss Marie Hammond of La Grange, Ga., in Fort Lauderdale, Fla., in October.

CLARENCE S. BOLENDER, Clearwater, Fla., to Mrs. Carrie Weaver Waddell of Cambridge City, Ind., September 18.

WILLIAM EDWARD STEINER, Savanna, Ill., to Miss Marie Melanie Kolbus of Chicago in September.

GROVER CLEVELAND WRENN, Siler City, N. C., to Miss Virginia Gaddy in Raleigh, October 20.

PLINY AUSTIN PRICE, Toledo, Ohio, to Miss Margaret Marie Harrigan of Columbus in October.

PHILLIP BROWER PARSONS, Charlotte, N. C., to Miss Annette Barnes of Elm City, October 12.

ERNEST DE WITT RICHARD PONZER to Miss Elizabeth Parkin, both of Chicago, September 21.

HENRY PLETCHER CLOSE to Miss Mary Dorothy Quinn, both of Philadelphia, October 1.

Deaths

Le Roy Long ✠ Oklahoma City; Louisville (Ky.) Medical College, 1893; member of the House of Delegates of the American Medical Association, 1903, 1904 and 1920; demonstrator of genito-urinary diseases at his alma mater, 1894-1895; dean and professor of surgery, University of Oklahoma School of Medicine, 1915-1931; past president of the Oklahoma State Medical Association and the Oklahoma County Medical Society; member of the Western Surgical Association and of the American Association for the Surgery of Trauma; fellow of the American College of Surgeons; member of the state board of medical examiners from 1911 to 1915; served during the World War; surgeon, St. Anthony's Hospital; aged 71; died, October 27.

Walter Edward List, Cincinnati; Medical College of Ohio, Cincinnati, 1907; member of the Ohio State Medical Association; superintendent of the Jewish Hospital; formerly superintendent of the Minneapolis General Hospital; trustee of the American Hospital Association from 1935 to 1937; on the editorial board of *Hospitals*, the Journal of the American Hospital Association; fellow of the American College of Hospital Administrators; aged 54; died, October 26, of coronary occlusion.

Frederick Woltmann, Kampsville, Ill.; Hahnemann Medical College and Hospital, Chicago, 1903; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1905; member of the Illinois State Medical Society; served during the World War; aged 64; died, October 7, in the Veterans Administration Facility, Jefferson Barracks, Mo., of melanotic sarcoma.

Edwin Minor Huston ✠ Dayton, Ohio; Medical College of Ohio, Cincinnati, 1896; past president of the Ohio State Medical Association and the Montgomery County Medical Society; formerly member of the board of education; for many years on the staff of the Miami Valley Hospital; aged 75; died, October 22, in Malone, N. Y., of carcinoma of the stomach.

George Washington Strickland, Roselle, N. J.; Long Island College Hospital, Brooklyn, 1895; member of the Medical Society of New Jersey; formerly member of the school board; aged 75; for many years on the staff of St. Elizabeth Hospital and Elizabeth General Hospital, Elizabeth, where he died, October 2, of cerebral hemorrhage and myocarditis.

Isadore Bernard Rothstein ✠ Newark, N. J.; University and Bellevue Hospital Medical College, New York, 1923; member of the American Academy of Pediatrics; aged 40; on the staff of the Irvington (N. J.) General Hospital, Babies' Hospital-Coit Memorial and the Newark Beth Israel Hospital, where he died, October 22, of malignant nephrosclerosis.

Louis Charles Deane ✠ San Francisco; Cooper Medical College, San Francisco, 1891; member of the Pacific Coast Oto-Ophthalmological Society; for many years visiting surgeon to the Stanford University Hospital; on the staff of the Mount Zion Hospital from 1912 to 1926; aged 69; died, October 17, of coronary occlusion and chronic myocarditis.

Frederick William Bailey, Manhasset, N. Y.; State University of Iowa College of Medicine, Iowa City, 1905; member of the American Academy of Ophthalmology and Otolaryngology; fellow of the American College of Surgeons; formerly on the staffs of St. Luke's and Mercy hospitals, Cedar Rapids, Iowa; aged 62; died, October 11.

Harry Clay Sharp, Lyons, N. J.; University of Louisville (Ky.) Medical Department, 1893; in 1909 delegate of the American Medical Association; served during the World War; at one time on the staff of the Indiana Reformatory, Jeffersonville, Ind.; on the staff of the Veterans Administration Facility; aged 70; died, October 31, of myocarditis.

Jacob Schultz, Middlesboro, Ky.; Hospital College of Medicine, Louisville, 1906; member of the Kentucky State Medical Association; past president of the Bell County Medical Society; on the staff of the Middlesboro Hospital; aged 60; died, October 3, in the Johns Hopkins Hospital, Baltimore, of septicemia and infection of the urinary tract.

Raymond Brewer Parker ✠ Winthrop, Mass.; Harvard Medical School, Boston, 1912; chairman of the board of health and school physician; president of the staff of the Winthrop Community Hospital; served during the World War; aged 54; died, October 19, of coronary thrombosis, arteriosclerosis, chronic nephritis and hypertension.

Hugh Alexander Chisholm, Halifax, N. S., Canada; McGill University Faculty of Medicine, Montreal, Que., 1905; served during the World War; at one time inspector of health of Nova Scotia and member of the department of pensions and national health; formerly port physician of Halifax; aged 57; died, September 25.

William John Bierer, Kittanning, Pa.; Western Pennsylvania Medical College, Pittsburgh, 1897; member of the Medical Society of the State of Pennsylvania; past president of the Armstrong County Medical Society; county medical director; for many years a member of the school board; aged 67; died in October.

James Lawrence Thompson, Columbia, S. C.; Medical College of the State of South Carolina, Charleston, 1880; member of the South Carolina Medical Association and the American Psychiatric Association; on the staff of the South Carolina State Hospital; aged 86; died, September 24, of arteriosclerosis.

William Bruce Almon, Halifax, N. S., Canada; Halifax Medical College, 1899; associate professor of obstetrics emeritus at his alma mater, now the Dalhousie University Faculty of Medicine; formerly visiting physician, Infectious Disease Hospital; at one time health officer; aged 65; died, September 11.

Albert Alton Getman ✠ Syracuse, N. Y.; New York Homeopathic Medical College and Flower Hospital, New York, 1915; fellow of the American College of Physicians; on the staff of the General Hospital; aged 52; died, October 28, in the Strong Memorial Hospital, Rochester, of cerebral arteriosclerosis.

Albert Clark Benedict, Yonkers, N. Y.; College of Physicians and Surgeons, medical department of Columbia College, New York, 1871; member of the Medical Society of the State of New York; for many years police surgeon; formerly on the staff of St. Joseph's Hospital; aged 96; died, October 29.

George Andrew Sarchet, Mobridge, S. D.; State University of Iowa College of Homeopathic Medicine, Iowa City, 1901; member of the South Dakota State Medical Association; served during the World War; on the staff of the Mobridge Hospital; aged 66; died, September 21, of carcinoma of the larynx.

Walter Redmon Pinnell, Mount Sterling, Ky.; University of Louisville (Ky.) Medical Department, 1907; member of the Kentucky State Medical Association; past president of the Montgomery County Medical Society; aged 54; died, October 2, in the Good Samaritan Hospital, Lexington, of nephritis.

Bruno Joseph Sawicki, Detroit; Toledo Medical College, 1913; Detroit College of Medicine and Surgery, 1917; member of the Michigan State Medical Society; served during the World War; aged 51; died, October 11, in the Mercy Hospital, Bay City, of injuries received in an automobile accident.

Simon Gunerus Gill, New Orleans; University of Louisiana Medical Department, New Orleans, 1878; at one time a pharmacist; formerly quarantine inspector for the state board of health at Port Eads, La.; aged 95; died, October 23, of malignant papilloma of the bladder and chronic myocarditis.

Francois X. L. de Martigny, Montreal, Que., Canada; School of Medicine and Surgery of Montreal, Faculty of Medicine of the University of Laval at Montreal, 1893; served during the World War; formerly on the staff of the Hôpital Ste. Jeanne d'Arc; aged 68; died, September 28.

Henry Bettis Malone, Chester, S. C.; North Carolina Medical College, Charlotte, 1909; member of the South Carolina Medical Association; served during the World War; was chairman of the county board of health; aged 65; died, October 8, of bronchiectasis and heart disease.

Donald Wallace Skeel ✠ Los Angeles; University of Southern California College of Medicine, Los Angeles, 1899; medical director of the Occidental Life Insurance Company; served during the World War; aged 67; died, October 11, of coronary thrombosis and arteriosclerosis.

David Kaufman, Altoona, Pa.; Jefferson Medical College of Philadelphia, 1908; member of the Medical Society of the State of Pennsylvania; served during the World War; aged 55; on the staffs of the Altoona Hospital and the Mercy Hospital, where he died, October 22, of leukemia.

Gustave A. Ozenne, Winfield, Ala.; University of the South Medical Department, Sewanee, Tenn., 1906; member of the Medical Association of the State of Alabama; aged 57; died, October 24, in a hospital at Birmingham of retroperitoneal hemorrhage and intestinal obstruction.

Abraham Turner Hubbell ✠ Wood River, Neb.; Chicago Homeopathic Medical College, 1903; Northwestern University Medical School, Chicago, 1905; aged 62; associate member on the staff of St. Francis Hospital, Grand Island, where he died, October 18, of coronary embolism.

Ralph Kable Collins, New York; Johns Hopkins University School of Medicine, Baltimore, 1922; member of the staff of the International Health Division of the Rockefeller Foundation; aged 46; died, October 1, at the Rockefeller Institute Hospital of pulmonary embolus.

Howard Wilbert Nowell ⊕ Brookline, Mass.; Boston University School of Medicine, 1911; instructor in pathology at his alma mater from 1911 to 1913 and associate professor from 1913 to 1915; aged 68; died, October 28, in Ogunquit, Maine, of chronic myocarditis.

John Aquaro, New York; Columbia University College of Physicians and Surgeons, New York, 1898; served during the World War; at one time inspector for the department of health, and physician on the staff of the department of correction; aged 64; died, October 15.

William Johnstone Thomson, Broadmoor, Colo.; Northwestern University Medical School, Chicago, 1899; member of the Colorado State Medical Society; served during the World War; aged 66; died, October 14, in the Glockner Hospital, Colorado Springs.

Samuel Augustus Scott, Eudora, Ark.; University of Louisville (Ky.) Medical Department, 1877; Medical Department of Tulane University of Louisiana, New Orleans, 1894; aged 87; died, October 14, in Vicksburg, Miss., of pernicious anemia and arteriosclerosis.

Clinton Durham Fife ⊕ Dayton, Ohio; Western Reserve University Medical Department, Cleveland, 1921; fellow of the American College of Physicians; on the staffs of the Miami Valley and Good Samaritan hospitals; aged 45; died, October 24, of uremia.

Lorin W. Smith, Hastings, Minn.; University of Pennsylvania Department of Medicine, Philadelphia, 1893; member of the Indiana State Medical Association; at one time mayor of Wabash, Ind.; aged 75; died, October 8, of chronic myocarditis and nephritis.

Gaston Torrance, Birmingham, Ala.; University of Virginia Department of Medicine, Charlottesville, 1897; member of the Medical Association of the State of Alabama and the Southern Surgical Association; aged 72; died, October 18, of pneumonia.

Archie L. Shanks, Hannibal, Mo.; Washington University School of Medicine, St. Louis, 1901; member of the Missouri State Medical Association; aged 65; on the staff of St. Elizabeth's Hospital, where he died, October 23, of coronary occlusion.

Leo Earle Wilson, Stamford, Conn.; University of Vermont College of Medicine, Burlington, 1928; member of the Connecticut State Medical Society; aged 37; died, October 13, of ruptured esophageal varices with hemorrhage and Laënnec's cirrhosis.

Dickson Leonard Moore, Columbus, Ohio.; University of Wooster Medical Department, Cleveland, 1892; member of the Ohio State Medical Association; for many years on the staffs of the Grant and Children's hospitals; aged 77; died, September 27.

Marian H. Frauenthal Sloane ⊕ New York; University and Bellevue Hospital Medical College, New York, 1930; on the staffs of the Hospital for Joint Diseases and the New York Infirmary for Women and Children; aged 35; died, September 23.

Allen Gilbert Ireland ⊕ Trenton, N. J.; Medical School of Maine, Portland, 1918; formerly member of the state department of public instruction; aged 40; died, October 23, in the University Hospital, Philadelphia, of glioma of the left temporal lobe.

William James Jolly ⊕ Oklahoma City; Medical College of the State of South Carolina, Charleston, 1882; an Affiliate Fellow of the American Medical Association; fellow of the American College of Surgeons; aged 91; died, September 24.

Elliott Thompson Jett, Falmouth, Va.; University of Virginia Department of Medicine, Charlottesville, 1889; aged 71; died, October 17, in the Mary Washington Hospital, Fredericksburg, of strangulated inguinal hernia and intestinal obstruction.

Samuel Ellsworth Blair, Alvord, Iowa; State University of Iowa College of Medicine, Iowa City, 1894; member of the Iowa State Medical Society; aged 73; died, October 8, in the McKennan Hospital, Sioux Falls, S. D., of coronary sclerosis.

Thomas H. Wood, Bell Buckle, Tenn.; University of Nashville Medical Department, 1886; member of the Tennessee State Medical Association; president of the Bedford County Medical Society; for many years mayor; aged 73; died, October 18.

James Coleman Fisher, Jefferson, Ohio; Rush Medical College, Chicago, 1889; on the board of trustees of Millikin University from 1904 to 1930; aged 82; died, October 27, in the Ingleside Hospital, Cleveland, of valvular heart disease.

Theodore Henry Smith, Detroit; Detroit College of Medicine, 1896; member of the American Urological Association; served during the World War; on the staff of the Harper Hospital; aged 65; hanged himself, September 30.

Wilmoth Osborne ⊕ New York; University of Oregon Medical School, Portland, 1924; on the staff of the New York Hospital; aged 44; died, September 12, in the Presbyterian Hospital of metastatic carcinoma of the brain.

Leslie Guy Eastman Hazen, N. D.; Hering Medical College, Chicago, 1903; member of the North Dakota State Medical Association; past president of the North Dakota Sixth District Medical Society; aged 67; died, September 21.

Leonard William Brown, Indianapolis; Central College of Physicians and Surgeons, Indianapolis, 1903; member of the Indiana State Medical Association; aged 64; died, October 5, in St. Vincent's Hospital of coronary occlusion.

Robert Henry Martin, Magnetic Springs, Ohio; McGill University Faculty of Medicine, Montreal, Canada, 1896; member of the Ohio State Medical Association; aged 65; died, October 30, in the University Hospital, Columbus.

Jessica Royce Carleton, Ambala, Punjab, India; Woman's Medical College of Pennsylvania, Philadelphia, 1886; medical missionary; for many years director of the Philadelphia Hospital for Women; aged 78; died, October 23.

James Leslie Passmore, Detroit; Michigan College of Medicine and Surgery, Detroit, 1906; veteran of the Spanish-American and World wars; aged 60; died, October 19, in the Receiving Hospital of cerebral hemorrhage.

Chester Dare Lee, Donelson, Tenn.; Vanderbilt University School of Medicine, Nashville, 1914; superintendent of the Tennessee Home and Training School for Feebleminded; aged 57; died, October 16, of cerebral hemorrhage.

Charles Frederick Roan ⊕ Chicago; University of Illinois College of Medicine, Chicago, 1928; on the staffs of the Augustana Hospital and the Lutheran Deaconess Hospital; aged 41; died, October 12, of coronary thrombosis.

Alan Greenleaf Terrell, Riverhead, N. Y.; College of Physicians and Surgeons, medical department of Columbia College, New York, 1892; formerly health officer; aged 74; hanged himself, October 9, in Southampton.

Edward J. Murphy ⊕ Philadelphia; Jefferson Medical College of Philadelphia, 1906; on the staffs of the Jewish Hospital, St. Mary's Hospital and the Germantown Dispensary and Hospital; aged 55; died, September 21.

Frederick Remington Johnson ⊕ New York; Columbia University College of Physicians and Surgeons, New York, 1936; aged 32; was killed, September 18, in an automobile accident near New Milford, Conn.

Virgil Dark, Opelika, Ala.; Medical Department of Tulane University of Louisiana, New Orleans, 1911; member of the Medical Association of the State of Alabama; aged 53; died, September 18, in Alexandria City.

Daniel H. Fondren, Maben, Miss.; Memphis (Tenn.) Hospital Medical College, 1893; member of the Mississippi State Medical Association; aged 71; died, October 13, in the Houston (Miss.) Hospital of heart disease.

Zachary Taylor Pinner, Pomaria, S. C.; Chattanooga (Tenn.) Medical College, 1905; member of the South Carolina Medical Association; aged 62; died, October 18, in a hospital at Columbia of pneumonia.

Raymond Clark Breece, Grand Rapids, Mich.; Michigan College of Medicine and Surgery, Detroit, 1906; served during the World War; aged 61; died, October 8, in the Michigan Soldiers' Home Hospital.

Anthony Joseph Villone, Quincy, Mass.; Tufts College Medical School, Boston, 1918; member of the Massachusetts Medical Society; aged 49; died, October 6, in the City Hospital of coronary thrombosis.

Richard Frederick Codrington, Richland, Mich.; McGill University Faculty of Medicine, Montreal, Que., Canada, 1902; aged 85; died, October 25, in the Borgess Hospital, Kalamazoo, of cirrhosis of the liver.

Lee Alfred Hays, Columbus, Ohio; Eclectic Medical College, Cincinnati, 1910; served during the World War; aged 58; died, October 30, in the White Cross Hospital, Columbus, of cerebral hemorrhage.

Clifford Gordon Engle ✠ Henderson, Texas; Eclectic Medical College, Cincinnati, 1920; aged 47; died, October 14, in a hospital at Natchitoches, La., of injuries received in an automobile accident.

Thomas James O'Brien, Pawtucket, R. I.; College of Physicians and Surgeons, Baltimore, 1912; on the staffs of the Homeopathic and St. Joseph's hospitals, Providence; aged 51; died, September 22.

Chester Ambrose Wilkinson ✠ Kendall, Mich.; Jefferson Medical College of Philadelphia, 1888; aged 78; on the staff of the Bronson Hospital, Kalamazoo, where he died, October 11, of heart disease.

John Charles Emme, Harlan, Ind.; Indiana University School of Medicine, Indianapolis, 1912; aged 50; died, October 25, in the Lutheran Hospital, Fort Wayne, of cardiovascular renal disease.

Laurence Clarke Swan ✠ Beverly, Mass.; Harvard Medical School, Boston, 1907; served during the World War; aged 59; on the staff of the Beverly Hospital, where he died, October 2, of embolism.

Walter V. Lunsford, Pueblo, Colo.; Ensworth Medical College, St. Joseph, Mo., 1891; aged 85; died, September 9, in the Parkview Hospital of acute myocarditis and pulmonary tuberculosis.

Charles Benjamin Shotwell, Richmond, Mo.; Rush Medical College, Chicago, 1883; member of the Missouri State Medical Association; aged 83; died, October 12, of bronchopneumonia.

Margaret O'Hara, Smith's Falls, Ont., Canada; Queen's University Faculty of Medicine, Kingston, 1891; for many years Presbyterian medical missionary in India; aged 85; died, August 27.

Tallulah S. Tucker, Memphis, Tenn.; Indiana Eclectic Medical College, Indianapolis, 1887; aged 78; died, September 21, in the Baptist Hospital of cholecystectomy following jaundice.

Ransom Lee Carr, Rosehill, N. C.; Baltimore Medical College, 1907; formerly member of the state legislature and county health officer; aged 62; died, October 17, of arteriosclerosis.

Robert Eugene Forster, Chicago; Magyar Királyi Erzsébet Tudományegyetem Orvostudományi, Pecs, Hungary, 1923; aged 40; was found dead, October 30, of poison, self administered.

Gisela Von Poswik ✠ Scranton, Pa.; Woman's Medical College of Pennsylvania, Philadelphia, 1911; member of the American Roentgen Ray Society; aged 65; died, October 2.

Le Roy Willis, Central City, Ky.; Kentucky University Medical Department, Louisville, 1905; member of the Kentucky State Medical Association; aged 58; died, September 5.

Francis Lawrence Oswald, New York; University of the City of New York Medical Department, 1894; veteran of the Spanish-American War; aged 75; died, September 27.

Harvey Alfred Berkes ✠ Los Angeles; Western Reserve University Medical Department, Cleveland, 1909; past president of the Hollywood Hospital; aged 58; died, October 30.

Raymond Eugene Robinson, Chicago; University Medical College of Kansas City, Mo., 1913; served during the World War; aged 50; died, October 2, of pulmonary embolism.

Charles Henry Curran, Springfield, Mass.; University of the City of New York Medical Department, 1886; died, September 10, of chronic myocarditis and arteriosclerosis.

James Rosser Bedford, Dahinda, Ill.; Rush Medical College, Chicago, 1881; Civil War veteran; aged 94; died, October 19, in Oneida of cerebral hemorrhage and pneumonia.

Charles E. Beitmen, Kendrick, Okla.; St. Louis College of Physicians and Surgeons, 1903; also a druggist; aged 73; died in October in Oklahoma City of cerebral hemorrhage.

James Alexander Murray, Victoria, B. C., Canada; Halifax (N. S.) Medical College, 1905; served with the Canadian Army during the World War; aged 59; died, August 27.

Frank Algan Duston, St. Stephen, N. B., Canada; Harvard Medical School, Boston, 1911; on the staff of the Chipman Memorial Hospital; aged 62; died, September 12.

Marion G. Wilbur, Chicago; Medical College of the State of South Carolina, Charleston, 1902; member of the Illinois State Medical Society; aged 68; died, October 8.

Eric Lafcadio Nye, Amarillo, Texas; University of Kansas School of Medicine, Kansas City, 1937; aged 30; died, October 24, of heart disease and pulmonary tuberculosis.

Frank Walter Shaw, Gimli, Man., Canada; University of Manitoba Faculty of Medicine, Winnipeg, 1920; aged 52; died, October 26, of hypertension and arteriosclerosis.

John R. Bolognino ✠ New York; Regia Università di Torino Facoltà di Medicina e Chirurgia, Italy, 1905; aged 59; died, October 22, of coronary thrombosis.

Eugene Young Amerson, Roscoe, Texas; University of Texas Faculty of Medicine, Galveston, 1939; aged 25; was killed, October 6, in an automobile accident.

Herman George Rosenblum ✠ Flint, Mich.; Toledo Medical College, 1913; served during the World War; aged 51; died, October 28, of myocarditis.

William S. Love, Wilber, Neb. (licensed in Nebraska in 1892); aged 90; died, September 30, in St. Elizabeth's Hospital, Lincoln, of arteriosclerosis.

William Park Myers, Anaheim, Calif.; Medical College of Ohio, Cincinnati, 1899 and 1906; aged 63; died, October 1, of hypertensive heart disease.

Louis William Eckels Jr., Louisville, Ky.; Kentucky University Medical Department, Louisville, 1906; aged 55; died, October 29, of pneumonia.

Arthur William West, San Antonio, Texas; Tulane University of Louisiana School of Medicine, New Orleans, 1919; aged 53; died, October 3.

Henry Michell De Werth, North Olmsted, Ohio; Cleveland Homeopathic Medical College, 1906; aged 60; died, October 21, of heart disease.

Orlando A. Hall, Webster City, Iowa; Eclectic Medical Institute, Cincinnati, 1876; aged 92; died, August 26, of cardiac vascular disease.

Cawood Johnson Carmichael ✠ Knoxville, Tenn.; Vanderbilt University School of Medicine, Nashville, 1902; aged 61; died, October 9.

Charles Henry Beadles, Oglesby, Ill.; Rush Medical College, Chicago, 1890; aged 73; died, October 2, in the Peoples Hospital, Peru.

John Ephraim Elliott, Toronto, Ont., Canada; Victoria University Medical Department, Coburg, 1884; aged 81; died, September 27.

Charles G. Main, St. John, N. B., Canada; McGill University Faculty of Medicine, Montreal, Que., 1891; aged 75; died, September 7.

James Holmes Barr, Yuba City, Calif.; Chicago Medical College, 1890; formerly county health officer; aged 82; died, September 9.

Alexander Jardine Hunter, Teulon, Man., Canada; University of Toronto Faculty of Medicine, 1895; aged 72; died, August 25.

James G. Pou, Courtland, Miss.; University of Louisiana Medical Department, New Orleans, 1871; aged 91; died, September 16.

Mary Gamble Bryson, La Jolla, Calif.; Trinity Medical College, Toronto, Ont., Canada, 1903; aged 66; died, September 4.

Hyuk Chong Liu ✠ Honolulu, Hawaii; College of Medical Evangelists, Los Angeles, 1922; aged 47; died, September 23.

Julia M. Walton, Jackson, Mich. (licensed in Michigan in 1900); aged 93; died, September 15, of cerebral hemorrhage.

Donald McKay, Collingwood, Ont., Canada; University of Toronto Faculty of Medicine, 1889; aged 74; died, September 28.

G. E. Bigham, Ivey, Ga.; University of the South Medical Department, Sewanee, Tenn., 1898; aged 65; died, September 25.

Cornelius Herman Van Ravenswaay ✠ Boonville, Mo. (licensed in Missouri in 1897); aged 69; died, September 29.

Lemuel Allen Carter, Bunnell, Fla.; Atlanta (Ga.) College of Physicians and Surgeons, 1909; aged 52; died, September 28.

Jacob Henry Siegel, Staten Island, N. Y.; Long Island College Hospital, Brooklyn, 1908; aged 57; died, October 24.

Alexander Moir, Hensall, Ont., Canada; Manitoba Medical College, Winnipeg, 1906; aged 66; died, September 12.

Franklin Beyersdorf, St. Helena, Calif.; Missouri Medical College, St. Louis, 1879; aged 87; died, September 13.

Frederick A. Luce, Cicero, Ill.; College of Physicians and Surgeons of Chicago, 1892; aged 84; died, October 2.

David Harold Karp, Rumson, N. J.; Long Island College Hospital, Brooklyn, 1908; aged 56; died, October 12.

John Nathan Thresh, Grand Bay, Ala.; Barnes Medical College, St. Louis, 1902; aged 66; died, October 14.

Correspondence

CLOSED METHOD OF TREATING COMPOUND FRACTURES

To the Editor:—I have just read with much interest the communication (THE JOURNAL, November 23, p. 1821) of Dr. De Groat of Detroit. All his references to the history of wound treatment are correct, but his account is still incomplete. In several of my contributions, going back to 1923, I have referred to the work of Ollier (1830-1900) in bone and joint surgery. As to wound treatment, actually he made no contribution whatever. All his suggestions about wound treatment had been anticipated by Magati (1579-1647) in Italy, Belloste (1654-1730) in France, John Hunter (1728-1793) in England and others.

The editorial in THE JOURNAL to which Dr. De Groat refers, and others relating to my work on the treatment of osteomyelitis, compound fractures and infected wounds, have to do not only with the treatment of wounds and fractures by infrequent dressings but with an entire program of preliminary immobilization, drainage operation, adequate immobilization in plaster of paris casts and infrequent dressings in the postoperative care. It is extremely important that this entire program be kept in mind, as the infrequent dressing method alone, while valuable in itself, is only a part of the program necessary for best results in cases of compound fracture.

In a recent discussion led by my associate Dr. Fritz Teal before the Boston Orthopedic Club (November 18) one of the members of the audience, Dr. Otto Herman, raised, among others, the following questions:

Q.—Do you ever have to do secondary wound suturing?
A.—We do no wound suturing in any case. The closing of contaminated pockets in any wound not only interferes with drainage but affords an opportunity in some cases for the development of anaerobic infections (gas gangrene, tetanus, and the like).
Q.—Does this Orr method stimulate granulation over bare bone areas (areas laid bare by injury)?
A.—In the early reduction, indirect skeletal fixation (or direct fixation in some cases) and infrequent dressing method that we employ, all these wounds heal from the bottom, as well as from the edges, by granulation. There are no pockets at all in the best cases and, while sinuses must occasionally be reopened, we almost never have to treat the wound by closure, skin graft or otherwise.
Q.—How do you treat compound fracture dislocation about joints?
A.—Such injuries are treated by immediate reduction, enlargement of wounds for drainage if necessary, petrolatum packs (into the wound but not into the joint), pins through adjacent bones and fixation of the limb in a cast.
Q.—Do you get infection at wire fixation points?
A.—We use rigid pins fixed in plaster of paris casts and have no irritation or infection either in the bone or in the skin.

Finally, our healed (or cured) cases have always constituted between 85 and 90 per cent of all our cases. The larger death and amputation rates in most reports are due usually to shock, to postoperative mixed infections due to dressings or to gas gangrene, most of which we avoid by the program I have proposed.

These questions indicate that even by such competent surgeons as Dr. Otto Herman, some of the points in my program (since 1923) are not fully appreciated. Obviously this is the case with Dr. De Groat. There is no reason whatever for associating Ollier's name with the infrequent dressing method. Many others have suggested that. The program which I propose, however, must be considered as a whole. It is different from any other treatment ever proposed for compound fractures, osteomyelitis and infected wounds in general.

H. WINNETT ORR, M.D., Lincoln, Neb.

To the Editor:—Dr. Albert De Groat suggests in a communication published in THE JOURNAL, Nov. 23, 1940, apropos of the editorial (THE JOUURNAL, September 21, p. 1022) under the heading "Closed Method of Treating Compound Fractures and Infected Wounds," that the credit for the method belongs to Ollier of Lyons and should be referred to as "Ollier's method." The originator of the method was not Ollier but Alphonse Guérin. He invented in the pre-Lister era the method of packing the wound thoroughly with cotton and bandaging it in a circular fashion sufficiently tight so as practically to accomplish immobilization. These bandages were left undisturbed for from twenty to twenty-five days. Guérin practiced this method on a wide scale at the Hôpital Saint Louis and accomplished a rate of recoveries truly miraculous for that period. Ollier introduced important modifications into the method of Guérin. Thus he sutured the stump after amputation and applied the cotton dressing above. He also applied Guérin's method in compound fractures with displacement of the fragments. In support of my statement I submit the following bibliographic references:

Chattelain, J. V.: Mémoire sur l'emploi du coton et des pansements rares dans le traitement des plaies et ulcères, *Rec. de mém. de méd. mil.* **39:** 61, 1836.
Courbet, A.; Alphonse Guérin; sa vie, son œuvre, Thesis, Paris, No. 45, 1913.
Alphonse Guérin, in Biographisches: Lexikon der hervorragenden Aerzte aller Zeiten und Völker, ed. 2, Berlin, 1930, vol. 2.
Hervey, A.: Pansement à la ouate, *Arch. gén. de méd.* **81:** 641, 1871.
Medical Milestones, *M. Rec.* **150:** 37 (July 5) 1939.
Rochard, J. E.: Histoire de la chirurgie française au XIX^e^ siècle, Paris, J. B. Baillière et fils, 1875.
Viennois: Combinaison des appareils inamovibles avec les pansements isolants dans le but d'obtenir la réunion immédiate, *Gaz. hebd. de méd.* **18:** 749, 1871.

GEORGE HALPERIN, M.D., Chicago.

PROSTIGMINE OF NO VALUE AS PREGNANCY TEST

To the Editor:—I wish to report my limited experience on the use of prostigmine in delayed menstruation. My results are not as favorable as those reported in the article of Soskin, Wachtel and Hechter in THE JOURNAL, May 25, on "Treatment of Delayed Menstruation with Prostigmine: A Therapeutic Test for Pregnancy."

Stimulated by the fine reports in the aforementioned article and the promotion of prostigmine methylsulfate by Hoffmann-LaRoche, I decided to use the test on a small number of private patients. The 4 cases tabulated give sufficient indication that their conclusions in only a small series of 25 cases are incorrect. Four interesting variations occurred, tending to indicate that prostigmine cannot be relied on as a test in a presenting case for diagnosis. The authors' statement "If she fails to menstruate, pregnancy may be diagnosed with the same degree of accuracy as in the Friedman test" is not true.

Results with Prostigmine Methylsulfate

Case	Friedman Urine Test	Prostigmine Methylsulfate, Ampules	Estradiol Benzoate, 2,000 Rat Units
1. V. N. aged 27; 14 days delayed; secundipara	Positive	3 × 2 cc. negative	No effect with 4 daily doses
2. M. B. aged 22; 21 days delay; primipara	Negative	Positive flow in 48 hrs. 2 cc.-2 cc.	.....
3. S. A. aged 24; 5 days delay; secundipara	Negative	Negative 3 × 2 cc.	Positive flow after 4 × daily dose
4. D. D. aged 21; 9 days delay; secundipara *	Negative	Negative 1 cc.-2 cc.-1 cc.	Not tried

* Patient clinically pregnant after a few weeks and is observed pending delivery.

In my first and second cases the results were confirming. My first patient gave a positive reaction to the Friedman test, with no response to prostigmine. The second had normal urine, and menstruation was produced with prostigmine. The results of the third and fourth cases disagreed. The third patient had normal urine which did not respond to prostigmine but did to estradiol benzoate. (The use of the latter I shall immediately explain). The fourth patient gave a negative reaction to a pregnancy urine test and no response to prostigmine but was found

to be pregnant clinically in a later examination. You will note four possible variations.

It will be noted that I used estradiol benzoate and it produced flow in a negative case and none in a positive one. I offer it as a suggestion in amenorrhea with a negative Friedman test. The technic I used was one ampule of 2,000 rat units daily for five doses. The flow will come during the injections or about two to four days after the last injection. How effective this treatment is I have not evaluated statistically.

ALEXANDER WINTER, M.D., New York.

"ILLUSTRATIVE ELECTROCARDIOGRAPHY"

To the Editor:—Some of the statements made by the reviewer of the book "Illustrative Electrocardiography" (THE JOURNAL, Sept. 21, 1940) are misleading. Some of the review presents debatable points on which I feel, on good authority, that our conclusions are much less theoretical and more logical than those of the reviewer.

The reviewer's criticism said: "It is questionable whether the attempt to locate the origin of the premature systole as stated on page 49 is correct." The great majority of recognized cardiologists agree with our interpretation (Nomenclature and Criteria for Diagnosis of Heart Disease, ed. 4, p. 128).

The review said: "It is doubtful whether the slight variation in the PR interval in plate 44 is worth mentioning." The variation is 0.02 second. This is certainly worth mentioning, as 0.02 second often means the difference between a normal record and a conduction block.

The review said: "The interpretation of plate 54 is wrong." Our conclusions were based on a comparison of records taken on a healthy young intern before and immediately following heavy exercise. The T wave prior to exercise was much smaller.

The reviewer said: "No useful purpose is served in showing the original lead 4 in plate 96, since this lead is no longer utilized." This is a misstatement of fact which no serious student of electrocardiography would uphold. True, the lead as such is no longer utilized, but, as the text explains, "A tremendous mass of literature has been published using the original fourth lead." Also a tremendous number of original fourth leads have been taken clinically. Furthermore, some of our noted authorities on the subject have incorporated the original fourth lead in their works and books. Both the research man and the clinician must know the basic picture from which precordial leads have evolved in order to evaluate properly the records of that time.

JULIUS BURSTEIN, M.D., New York.

CRYSTALLIZATION (?) OF METALS

To the Editor:—My attention has been called to a medicolegal abstract ("Malpractice: Liability for Injury to Patient from Nurse's Operation of Fluoroscope") in THE JOURNAL, September 28.

The National Bureau of Standards letter circular LC486, "Metals Do Not 'Crystallize' Under Vibration," has been prepared to answer the many inquiries we receive on this subject.

Members of the staff of the National Bureau of Standards are called on to examine many instances of fatigue failure in all sorts of structures. It is our experience that one fatigue failure in a certain part in a given structure which has been in use for a considerable time is all too likely to be followed by a number of like failures in the same part in other structures of the same kind which have given as long or longer similar service.

This likelihood is so great that it is frequently thought advisable in the case of a serious fatigue failure in one airplane to ground all airplanes of the same kind until they can be examined to make absolutely sure that there is no cause to anticipate other failures of the same kind or, if cause is found, to remove it.

A roentgen ray examination is useless, since fatigue failures are not caused by crystallization.

The examination consists in looking for such surface defects as are mentioned in the letter circular, corrosion pits or other notches, abrupt changes in section, sharp reentrant angles, roughly machined surfaces and the like, and in addition a careful inspection for any fatigue cracks which may have started. For steel parts an inspection by means of finely divided magnetic particles, either as a dust or suspended in oil (commercially known as Magnaflux), is now routine practice when fatigue cracks are feared.

If, as is implied in the report of this case, the failure was a fatigue failure, and serious personal injuries might result from like failures in other fluoroscopic tables of the same kind, it would seem to me very desirable that all tables of that particular model and other models having the same mechanism should be carefully examined as just outlined.

If a second accident of the same kind should occur, it would seem to me, in view of this previous failure, difficult to maintain that the maker and users of the apparatus had exercised proper care to prevent it.

L. B. TUCKERMAN, Washington, D. C.
Assistant Chief, Mechanics and Sound Division,
National Bureau of Standards.

[COMMENT.—The medicolegal abstract that prompted this correspondence involved liability for injuries sustained by a patient because of the failure of a fluoroscopic table to operate properly. A representative of the manufacturer of the table investigated the accident and testified in court that a broken pin was the causal factor and further that the "parts showed it was broken from crystallization." Among other contentions, the plaintiff urged that the defendants had not from time to time caused the gear box to be taken off, the gears to be removed or the pin to be taken out of its socket and placed under roentgenrays to determine whether crystallization had occurred. For further details with respect to this case readers are referred to the abstract of it, which was published in THE JOURNAL, September 28, page 1128.—ED.]

DEATH OF DR. R. FORTESCUE FOX

To the Editor:—Your London staff correspondent in his letter of August 11 (THE JOURNAL, September 21) ends with mention of the recent death of England's leading balneologist, Dr. Robert Fortescue Fox. Unfortunately, he mixed the latter's fine life record with that of a relative, Dr. Richard Hingston Fox, noted in another special field of practice.

Fortescue Fox was one of Britain's pathfinders in physical medicine, his manual on "Physical Remedies for Disabled Soldiers," to refer to only one of his authoritative writings, proving of great help to those of us stationed in hospitals during the first world war.

The concluding statement of your overseas correspondent, "A great pioneer of physical therapy, he experienced much of the disappointment of the reformer in a world which will not share his enthusiasms," may apply to conservative England but no longer to North America. Over here, aided by the American Medical Association, our profession grows ever more aware of the usefulness of modern physical treatment methods.

In later years the activities of Fortescue Fox were largely directed to thalassotherapy and balneotherapy, his editorial charge of the *Archives of Hydrology* bringing him in touch with physicians of many countries interested in spa treatment and, especially, rheumatic conditions.

Long acquaintance and admiration for the many sided talents of this leader in our profession is my warrant for this brief tribute.

A. BERN HIRSH, M.D., New York.

Queries and Minor Notes

THE ANSWERS HERE PUBLISHED HAVE BEEN PREPARED BY COMPETENT AUTHORITIES. THEY DO NOT, HOWEVER, REPRESENT THE OPINIONS OF ANY OFFICIAL BODIES UNLESS SPECIFICALLY STATED IN THE REPLY. ANONYMOUS COMMUNICATIONS AND QUERIES ON POSTAL CARDS WILL NOT BE NOTICED. EVERY LETTER MUST CONTAIN THE WRITER'S NAME AND ADDRESS, BUT THESE WILL BE OMITTED ON REQUEST.

FIRE AND EXPLOSIVE HAZARD IN PRESENCE OF OXYGEN ADMINISTRATION

To the Editor:—**I recently gave an order at the hospital for continuous steam inhalation and oxygen administration by catheter. The sister on duty told me that doctors in another hospital had forbidden her to administer oxygen and steam inhalation in the room at the same time. She also said that persons visiting patients receiving oxygen were not permitted to smoke. Is there any reason for such a rule? Is there any danger of explosion when a person smokes in the same room in which oxygen is being administered? If there are any contraindications to these various procedures please tell me about them and also the mechanism involved.**

V. V. Anderson, M.D., Del Norte, Colo.

ANSWER.—The 20 per cent oxygen in atmospheric air is responsible for the burning of all fuels and other oxidizable substances. As the percentage of oxygen is increased, the ease with which combustion occurs increases rapidly, while the degree of heat necessary for ignition becomes less. Oxygen itself does not burn or explode from contact with a source of heat. Although a glowing heat source is necessary to ignite some materials (sheets, blankets and the like) even in high oxygen atmospheres, some substances (such as lint or organic dusts) may burn or even explode in the presence of high oxygen concentrations when exposed to moderate degrees of heat. In particular ether, vinethene, cyclopropane and ether, exhaled by the patient in the hours immediately after operation, are a great danger.

Steam is usually produced by stoves or electrical heating elements. Such sources of heat should be banned from the room of a patient receiving any form of oxygen therapy. Simultaneous administration of oxygen and steam is not harmful of itself, provided the source of heat for the latter is remote. Steam from a radiator or stem pipe or jugs of hot water is quite safe.

Smoking must be prohibited in the room where oxygen is being administered. The glowing pipe, cigar or cigaret might suddenly flare into violent flame if brought close to the patient or if air currents carried excess oxygen toward the smoker.

VACCINE VIRUS AND IMMUNITY TO POLIOMYELITIS

To the Editor:—**Is there any experimental evidence or are there statistical data that vaccinia confers any immunity against infantile paralysis? Such a phenomenon seems possible to me. Vaccinia causes immunity to variola and to herpes virus. Moreover, mouse infantile virus protects monkeys against lethal doses of monkey virus. Might not extensive smallpox vaccination be worth trying as a protective measure in an epidemic of infantile paralysis?**

Richard E. Stifel, M.D., Cleveland.

ANSWER.—There is no evidence that the vaccine virus confers immunity against poliomyelitis. This subject has been investigated on several occasions. In the early years, soon after the discovery of and isolation of the virus (Thompson, O.: *Berl. klin. Wchnschr.* **49**:63, 1912, **51**:309, 1914; *Ztschr. f. Immunitätsforsch.* **14**:198, 1912), neither immunity nor alterations in the course of experimental disease were produced when the virus of vaccinia and the poliomyelitis virus were applied together on the skin. Thompson believed, however, that the poliomyelitis virus proliferated in the pustules. Hurst and Fairbrother (*Brit. J. Exper. Path.* **12**:17, 1931) also concluded that the neurovaccine had no power to modify the poliomyelitis lesions in the nervous system regardless of the route of inoculation. It is known that school children who are still active in their immunity against vaccinia are just as susceptible to attacks of poliomyelitis as are children not vaccinated. These data were obtained in the Chicago and Illinois epidemics of 1936 and 1937. The status of the new cotton rat virus (Armstrong and Jungeblut) as an immunizing agent against the monkey virus has not been determined conclusively as yet.

In summary, there is no evidence that vaccination against smallpox leads to protection in an epidemic of infantile paralysis. The only positive ray of hope in protection against this disease appears to come from the recent work showing that the virus is contained in sewage and intestinal discharges of carriers and active cases, including both paralytic and nonparalytic types. This would indicate the usual precautions which are used in the prevention of wholesale dissemination of intestinal borne diseases, including boiling of water and the prevention of congregations of children where an aqueous medium may disseminate the disease, such as swimming pools. Chlorination and other chemicals appear to have little effect on the virus.

HEREDITARY DYSTROPHY OF HAIR AND NAILS

To the Editor:—**I wish to inquire about nonsyphilitic baldness showing for three direct generations. There is scarcely a trace of hair and only rudimentary finger and toe nails. 1. How often is this found? 2. What may be the cause? 3. Are such individuals usually normal physically and mentally? 4. Is it similar to albinism? 5. Kindly give the history of this condition.**

M.D., Iowa.

ANSWER.—1. Cases of this type are rare and should therefore be studied and accurately recorded. The heredity should be worked out as clearly as possible, the condition of the hair, nails, teeth, skin and eyes carefully noted, and a general examination of the patient for any indications of metabolic or endocrine anomalies should be made.

2. Consanguinity of the parents has been recorded in several instances and of course this adds to the probability of the occurrence of this defect in the children. Many cases have no such easy explanation and in some the case recorded is the only one in the family, so far as known. Henry Joachim (Dystrophy of the Hair and Nails in Six Generations, *Ann. Int. Med.* **10**:400 [Sept.] 1936) reports this dystrophy in nineteen of forty-two individuals in six generations of a family. In one of his cases there had been defective vision since childhood but the eye clinic reported only that the visual field of the left eye was contracted. One authority states that the partial types are of dominant heredity, while another holds that the generalized type is recessive. This is one of the reasons for urging the study of all such cases.

Besides the involvement of the teeth and nails, so common an accompaniment of alopecia congenita, eye defects, webbing of the fingers and toes, atrophy of parts of the skin, epidermolysis bullosa and alopecia areata have been recorded. J. N. Hyde, early among American writers on this condition (Congenital Alopecia as an Expression of Atavism, *J. Cutan. Dis.* **27**:1, 1909), cited cases in his own practice, one of webbed fingers and toes and another of opaque patches in the retina. He also mentioned Eschner's case with exaggerated myopia and white areas in the retina. Jäckli (Ein Fall von infantiler Poikiloderma, [Atrophodermia Reticularis cum Incontinentia Pigmenti] kombiniert mit Alopecie, Mikrodentie und frühseitiger Cataracta Complicata, *Monatschr. f. Kinderh.* **78**:73 [March 24] 1939) reports a case of severe atrophy of the skin and bilateral juvenile cataract in a little girl whose hair, normal at birth, fell out before she was 3 weeks old and never regrew. One of Hyde's patients had xeroderma, and he mentions this complication in the case of Guilford and Luce. He also mentions Wende's case with atrophy of the finger tips and congenital epidermolysis bullosa.

3. All authorities agree that these patients show mental and physical defects, other than those mentioned in connection with the baldness, no more frequently than individuals without the ectodermal dystrophies.

4. The only similarity between this group of ectodermal defects and albinism is that both are hereditary. Albinism is a defective formation of pigment in the skin, iris and hair, often accompanied by mental and physical weakness. There is no other abnormality of the skin, hair, nails or teeth; thus albinism differs sharply from the condition mentioned in the query.

5. By "the history of this condition" it is inferred that the prognosis is meant. The best way to answer this question is to get a biopsy of the scalp. If only the merest traces of hair follicles are found, as recorded by some investigators for their cases, no hope can be given that hair will grow later. If, however, many bed hairs are seen, there is a possibility that the hair can be restored. Every encouragement should be given the patient to continue for a long time the use of local stimulants to the scalp such as are used for other types of alopecia. Ultraviolet rays in erythema doses given once or twice a week, depending on the amount of irritation caused, are an excellent stimulant; but the acquired resistance soon makes it necessary to give long treatments. Then chemical irritants may succeed it; a mixture of equal parts of tincture of iodine, chloral hydrate and phenol can be painted on once a week. One part of phenol with four parts of lactic acid is also effective. Solutions of cresol in alcohol can be used in increasing strength, beginning

with 25 per cent and going to 90 per cent. Chrysarobin in varying strength is also recommended; but great care must be exercised that none of the preparation gets into the eyes. It is well not to use these irritants at once over the whole scalp but to try out their effect first on a small area. During intervals of rest from the strong treatment milder stimulants may be used, salicylic acid and sulfur in ointment, mercurials in ointment or alcoholic solution.

COMBINED FEVER AND ROENTGEN THERAPY FOR CANCER

To the Editor:—I understand that some work is being done on carcinoma at Rochester, N. Y., with the use of high voltage roentgen therapy combined with a special type of short wave therapy. Can you furnish me with any information about this?

A. L. Goldwyn, M.D., South Ozone Park, N. Y.

ANSWER.—Studies on the combined effects of high voltage roentgen therapy and artificial fever on carcinoma are under way at Rochester, N. Y., and probably elsewhere too.

The summative effects of the two radiations x-rays and heat appear to be more destructive to the carcinoma and normal structures than either alone. Since the dosage values are not well understood the experiments have been restricted to hopeless cases. The delayed effects (telangiectases, edema, cutaneous degeneration, and the like) seem to be more marked, probably because of the summative effect.

The following dosage has been used with safety, though it should not be attempted by any one not well versed in both irradiation technic and fever treatment technic: Daily for six days 250 roentgens is given in the usual manner for any one port. On the third day in this schedule a five hour fever bout at 41.5 C. (106.7 F., rectal temperature) is administered and at the end of the fever, while the body temperature is up, that day's x-ray treatment is given. A second fever bout of one hour (or more if the patient is not too much intoxicated by the tumor destruction) is given on the fifth day with the x-ray treatment again administered at its end. Several portals may be treated simultaneously except that great caution must be exercised not to overtreat (i. e. not over 1,800 roentgens given to any one skin area) within a given course. Courses have been repeated in six months without catastrophe, although the damage to the skin was considerable.

At present this method is purely experimental and is not advocated for general use until its merits are more clearly defined.

MINERAL METABOLISM AND ELECTROLYTE BALANCE

To the Editor:—I am interested in the relation of mineral salt metabolism or, let me say, electrolyte metabolism and disease. As a matter of routine in medical conditions I elicit a dietary history from my patients and I find that the incidence of faulty eating and the preparation of foods is appalling. I should therefore like to know if any reports have been published on investigative work giving this relationship quantitatively and qualitatively. In the literature there is often mentioned the term "electrolyte pattern." Just exactly what is meant by that term? References on this most interesting subject will be greatly appreciated.

B. C. Baron, M.D., Munising, Mich.

ANSWER.—The best outline of this subject is probably to be found in the recently published monograph by A. T. Shohl on "Mineral Metabolism" (published by the Reinhold Publishing Corporation), reviewed in THE JOURNAL, April 27, page 1691. The phrase "electrolyte pattern" is subject to considerable individual interpretation. However, in general it refers to the complex interrelations of the ions of electrolytes such as the direct relation between sodium and chlorine in the tissues and the inverse relation of sodium and potassium. A good discussion for the interested physician may be found in an article by A. M. Butler on "Electrolyte and Water Balance" (*New England J. Med.* **220**:827 [May 18] 1939).

COAL OIL INSTILLATIONS FOR ULCERATIVE COLITIS

To the Editor:—Has the use of coal oil by instillation in chronic ulcerative colitis been tried in competent hands? If so what quantity is used and what results have been obtained?

M.D., California.

ANSWER.—From twelve to fifteen years ago coal oil instillations into the rectum received intensive trial in cases of amebic dysentery. At the time this was used in the treatment of amebiasis and amebic colitis it was also employed in other types of chronic ulcerative colitis. It was found to be too irritating and was soon abandoned as having no great value and possibly associated with some hazard. Coal oil is irritating to the skin and so when it was being instilled it was found necessary to grease the parts about the rectum with petrolatum. The amount instilled was about a pint. Injections were given every second day for a period of twenty-eight days.

POSSIBLE ARSENIC IN MILK AND ABORTION

To the Editor:—What form of arsenic preparation is used for spraying weeds and grass? If cattle should eat the grass which has been sprayed with an arsenic preparation would arsenic be found in the cow's milk in sufficient quantity to cause an acute poisoning with severe diarrhea and a miscarriage in a woman about four months pregnant? A woman claims that such a case has occurred. The cows that ate this sprayed grass died. The cows were milked a few hours after eating the grass and the woman drank this milk. A few hours later she had severe diarrhea and abdominal cramps. She was about four months pregnant. She miscarried and has been in poor health since.

Bernard Patrick, M.D., Corinth, Miss.

ANSWER.—There are several forms of arsenic for spraying weeds and grass—sodium arsenate, sodium arsenite, calcium arsenate and lead arsenate. In the South large amounts of calcium arsenate are used, particularly on cotton fields. There is no indication in this query what form of arsenic was used. If arsenic is eaten, some of it may appear in the milk so that it is possible that some arsenic could be obtained in this way, and arsenic may produce diarrhea and cramps. That this diarrhea might produce an abortion is possible,. but without further evidence on the subject one cannot say more than that it is possible.

ALCOHOL BY WEIGHT AND BY VOLUME

To the Editor:—In recent months there have been frequent references to 70 per cent alcohol by weight and the greater effectiveness of this concentration as an antiseptic. What would be the volumetric equivalent of this concentration?

M.D., Illinois.

ANSWER.—There can be no constant volumetric equivalent for 70 per cent alcohol by weight unless three variables are controlled:

1. Temperature. Alcohol is so expansile that 70 Gm. of it when warm occupies a larger volume than the same 70 Gm. when cool; water, on the other hand, has a relatively low coefficient of temperature expansion. Consequently 70 per cent by weight (that is, 70 Gm. of alcohol plus 30 Gm. of water) at 15 C. is equivalent to about 76.9 per cent by volume, whereas at 30 C. it is equivalent to about 82.5 per cent by volume.

2. Reaction contraction. When alcohol and water are combined, the resultant solution contracts with production of heat and the total volume decreases further as the solution cools. Hence it makes a difference whether alcohol and water are both measured separately before mixing or whether only the alcohol is measured and water is added to bring the total volume up to a certain level.

3. Alcohol content of commercial alcohol. Different lots of commercial alcohol have been found to vary between 95 and less than 92 per cent by volume.

If these three variables are not appreciated and controlled, it is possible that the volume per cent equivalent of "70 per cent alcohol by weight" may lie anywhere between 75 and 84. Or, to put it another way, 76.9 per cent by volume (or any other set figure) as ordinarily prepared may miss by a considerable margin being 70 per cent by weight. The reason for the discrepancy is that alcohol solutions by weight are unaffected by these variables and therefore are absolutely uniform. A somewhat fuller discussion of this matter is contained in an article entitled Ethyl Alcohol as a Germicide, by Dr. Philip B. Price, in the *Archives of Surgery* **38**:528 (March) 1939.

HOT FOODS AND GASTROINTESTINAL CANCER

To the Editor:—Is there any method of preventing cancer of the stomach and bowels? Are too hot drinks and food a factor in causing it?

M.D., Pennsylvania.

ANSWER.—There is no known method of preventing cancer of the stomach and intestine. Hot foods have been suspected as having an etiologic relationship to cancer of the stomach but there is no positive evidence to prove this relationship. Many observers believe that hot and irritating foods constitute one factor in the development of gastric cancer but the relative importance of this factor is not definitely known.

TESTS FOR HOMOSEXUAL TENDENCIES

To the Editor:—In The Journal of September 28, 1940, on page 1122, I notice a reply to an inquiry about possible homosexual tendencies. I should like to suggest in addition to the routine psychiatric examinations and textbooks that are recommended the utilization of projective tests. Examination by means of the Rorschach test and the Szondi test could easily give much more complete and adequate information than any formal psychiatric examination could yield—that is, provided the tests are given by some person fully qualified to administer and interpret them.

Milton H. Erickson, M.D., Eloise, Mich.

Medical Examinations and Licensure

COMING EXAMINATIONS

BOARDS OF MEDICAL EXAMINERS
BOARDS OF EXAMINERS IN THE BASIC SCIENCES

Examination of boards of medical examiners and boards of examiners in the basic sciences were published in THE JOURNAL, December 7, page 2019.

NATIONAL BOARD OF MEDICAL EXAMINERS

NATIONAL BOARD OF MEDICAL EXAMINERS: Parts I and II. Various centers, February 10-12. Exec. Sec., Mr. Everett S. Elwood, 225 S. 15th St., Philadelphia.

EXAMINING BOARDS IN SPECIALTIES

AMERICAN BOARD OF ANESTHESIOLOGY: *Written.* Various centers, Feb. 20. Final date for filing application is December 21. *Oral.* Part II. Cleveland, May 31-June 1. Final date for filing application is April 1. Sec., Dr. Paul M. Wood, 745 Fifth Ave., New York.

AMERICAN BOARD OF INTERNAL MEDICINE: *Written.* Parts 1-A and 1-B, Feb. 17. Final date for filing application is Jan. 1. Sec., Dr. William S. Middleton, 1301 University Ave., Madison, Wis.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY: Part II, Groups A and B, Cleveland, May 28-June 1. Final date for filing application is March 15. Sec., Dr. Paul Titus, 1015 Highland Bldg., Pittsburgh.

AMERICAN BOARD OF OPHTHALMOLOGY: *Oral.* Cleveland, May or June. Sec., Dr. John Green, 6830 Waterman Ave., St. Louis.

AMERICAN BOARD OF PATHOLOGY: *Oral and Written.* Cleveland, June 1-2. Final date for filing application is May 1. Sec., Dr. F. W. Hartman, Henry Ford Hospital, Detroit.

AMERICAN BOARD OF PEDIATRICS: New York, March 30-31, following the Region I meeting of the American Academy of Pediatrics. Chicago, May 18, following the Region III meeting of the American Academy of Pediatrics. Sec., Dr. C. A. Aldrich, 723 Elm St., Winnetka, Ill.

AMERICAN BOARD OF RADIOLOGY. *Oral.* Cleveland, May 30-June 1. Final date for filing application is April 15. Sec., Dr. Byrl R. Kirklin, 102-110 Second Ave., S.W., Rochester, Minn.

Indiana June Report

Dr. J. W. Bowers, secretary, Indiana State Board of Medical Registration and Examination, reports the written examination for medical licensure held at Indianapolis, June 18-20, 1940. The examination covered fifteen subjects and included 100 questions. An average of 75 per cent was required to pass. One hundred and eighteen candidates were examined, all of whom passed. The following schools were represented:

School	PASSED	Year Grad.	Number Passed
College of Medical Evangelists		(1940)	1
Yale University School of Medicine		(1939)	1
Loyola University School of Medicine		(1940, 3)	3
Northwestern University Medical School		(1940)	1
Rush Medical College		(1939)	1
University of Illinois College of Medicine		(1940, 2)	2
Indiana University School of Medicine	(1938), (1939), (1940, 100) 102		
University of Louisville School of Medicine		(1940, 2)	2
Johns Hopkins University School of Medicine		(1938)	1
Columbia University College of Physicians and Surgeons		(1940)	1
University of Oregon Medical School		(1939)	1
Marquette University School of Medicine		(1940)	1
Friedrich-Wilhelms-Universität Medizinische Fakultät, Berlin		(1937)	1

Washington July Report

Mr. Nelson N. Vaughan, secretary, Department of Licenses, reports the written examination for medical licensure held at Seattle, July 15-17, 1940. The examination covered 7 subjects and included 70 questions. An average of 60 per cent in each subject was required to pass. Thirty-five candidates were examined, all of whom passed. Twenty-six physicians were licensed to practice medicine by reciprocity and 8 physicians so licensed by endorsement. The following schools were represented:

School	PASSED	Year Grad.	Per Cent
Stanford University School of Medicine		(1939)	87.8*
George Washington University School of Medicine		(1939)	84.3
Loyola University School of Medicine	(1939) 89.1, (1940) 78.2,		83.3
Northwestern University Medical School	(1935) 82.3, (1937) (1938) 82.1, 92.1, (1940) 81.1, 85.5†		87,
Rush Medical College	(1921) 80.6, (1937) 82.1,	(1939)	79.5
University of Illinois College of Medicine		(1940)	79, 87
Indiana University School of Medicine		(1933)	73
University of Michigan Medical School	(1934) 82.6, (1936) (1939) 85.3		85.3,
Washington University School of Medicine		(1939)	78.1
Creighton University School of Medicine		(1939)	70.8
Columbia University College of Physicians and Surgeons		(1939)	86.3
University of Oregon Medical School		(1939)	81, 81, 83.1, 83.2, 84, 85.3, 85.3, 89.3
McGill University Faculty of Medicine		(1939)	79
Medizinische Fakultät der Universität Wien		(1934)	78
Universität Heidelberg Medizinische Fakultät		(1909)	81.5
Universität Bern Medizinische Fakultät		(1937)	76.1

School	LICENSED BY RECIPROCITY	Year Grad.	Reciprocity with
College of Medical Evangelists		(1938)	California
Stanford University School of Medicine		(1937)	California
University of California Medical School		(1936)	California
Loyola University School of Medicine		(1936)	Missouri
Northwestern University Medical School		(1939)	California
Rush Medical College	(1937) Oregon, (1938),	(1939)	California
University of Maryland School of Medicine and College of Physicians and Surgeons		(1925)	Maryland
University of Minnesota Medical School	(1928),	(1940)	Minnesota
St. Louis University School of Medicine		(1937)	Missouri
Washington University School of Medicine	(1932),	(1933)	Missouri
Creighton University School of Medicine	(1938),	(1939, 2)	Nebraska
University of Nebraska College of Medicine	(1932),	(1939, 2)	Nebraska
Cornell University Medical College		(1937)	Oregon
University of Oklahoma School of Medicine		(1939)	Oklahoma
University of Oregon Medical School (1938) California, Minnesota		(1936)	Oregon,
University of Wisconsin Medical School		(1937)	Wisconsin

School	LICENSED BY ENDORSEMENT	Year Grad.	Endorsement of
College of Medical Evangelists	(1937),	(1940)	N. B. M. Ex.
University of Kansas School of Medicine		(1933)	N. B. M. Ex.
Duke University School of Medicine		(1937)	N. B. M. Ex.
University of Oregon Medical School		(1937), (1939)	N. B. M. Ex.
University of Pennsylvania School of Medicine		(1936)	N. B. M. Ex.
Marquette University School of Medicine		(1935)	N. B. M. Ex.

* This applicant has completed four years' medical work and will receive the M.D. degree on completion of internship. License has not been issued.

† License has not been issued.

Tennessee September Report

Dr. H. W. Qualls, secretary, Tennessee State Board of Medical Examiners, reports the written examination for medical licensure held at Memphis, Sept. 25-26, 1940. The examination covered 10 subjects and included 100 questions. An average of 75 per cent was required to pass. Twenty-seven candiates were examined, all of whom passed. The following schools were represented:

School	PASSED	Year Grad.	Per Cent
University of Rochester School of Medicine and Dentistry		(1940)	83.7
Meharry Medical College		(1929) 82.3, (1938)	85.3
University of Tennessee College of Medicine	(83.5, 83.5, 84, 84.5, 84.6, 84.8, 85.2, 85.3, 85.4, 85.6, 85.7, 86.1, 86.2, 86.5, 86.7, 87.1, 87.3, 87.7, 87.7, 88, 88.5, 88.8	(1940)	82.7,
Vanderbilt University School of Medicine		(1939)	84

Thirteen physicians were licensed to practice medicine by endorsement from August 5 through October 11. The following schools were represented:

School	LICENSED BY ENDORSEMENT	Year Grad.	Endorsement of
College of Medical Evangelists		(1939)	California
University of Georgia School of Medicine		(1938)	Georgia
State University of Iowa College of Medicine		(1938)	Iowa
Tulane University of Louisiana School of Medicine		(1919)	Louisiana
Johns Hopkins University School of Medicine		(1933)	N. Carolina
Harvard Medical School		(1928)	N. B. M. Ex.
Washington University School of Medicine		(1936)	Missouri
New York Homeopathic Medical College and Flower Hospital		(1933)	New Jersey
Duke University School of Medicine		(1935)	Minnesota
Temple University School of Medicine		(1937)	Penna.
Baylor University College of Medicine		(1938)	Texas
Univ. of Virginia Department of Medicine	(1930),	(1933)	Virginia

Vermont June Report

Dr. W. Scott Nay, secretary, Vermont State Board of Medical Examiners, reports the written examination for medical licensure held at Burlington, June 11-13, 1940. The examination covered 12 subjects and included 90 questions. An average of 75 per cent was required to pass. Eighteen candidates were examined, all of whom passed. The following schools were represented:

School	PASSED	Year Grad.	Per Cent
University of Vermont College of Medicine	(1939)* 88.9, (1940)* 86.2, 86.6, 87.1, 87.1, 87.8, 88, 88.1, 88.6, 88.6, 88.9, 89.3, 90, 90.4, 91.8, 92.9	(1938)	85.3,
Universidad Central de España Facultad de Medicina, Madrid		(1933)	75.1

Six physicians were licensed by endorsement from February 26 through August 3. The following schools were represented:

School	LICENSED BY ENDORSEMENT	Year Grad.	Endorsement of
College of Medical Evangelists		(1938)	Wisconsin
Tufts College Medical School		(1938)	N. B. M. Ex.
Columbia Univ. College of Physicians and Surgeons		(1934)	New York
Cornell University Medical College		(1932)	N. B. M. Ex.
University of Vermont College of Medicine	(1937),	(1939)	N. B. M. Ex.

* Licenses have not been issued.

Book Notices

Graduate Medical Education. Report of the Commission on Graduate Medical Education. Cloth. Pp. 304. Chicago: University of Chicago Press, 1940.

The Commission on Graduate Medical Education was organized in 1937 as an offshoot of the Advisory Board for Medical Specialties, which felt that it was more representative of the different interests involved than any other body. The commission's activities were financed by the Rockefeller Foundation, the Carnegie Foundation, the Josiah Macy Jr. Foundation and some smaller contributions from other groups. Concerning internship it concludes:

1. The internship should be regarded as a part of the basic preparation for either beginning the general practice of medicine or undertaking advanced training in a specialty.

2. The internship should provide a real educational experience and a period of clinical responsibility under supervision that is designed to complete the clinical clerkship of the medical course.

3. The internship should be an important responsibility of the staff and should be under the direction of those members who are competent to provide the necessary instruction.

4. The internship should be a joint responsibility of the medical schools and of those hospitals that can provide a satisfactory completion of the fundamental preparation for medical practice.

Of residencies it says:

1. The residency should be the most satisfactory method of graduate training for specialized fields of practice.

2. The residency should be organized as a real educational experience provided by qualified teachers who are willing to assume responsibility for adequate instruction.

3. The residency should provide preparation in the sciences basic to the specialty as well as sufficient clinical experience, under supervision, to ensure real competence.

4. The residency should be a joint responsibility of medical schools and of those hospitals able to provide residencies of a satisfactory educational character.

The following are stated to be the basic principles of postgraduate medical education:

1. Postgraduate medical education should aim to keep the physician abreast of current knowledge in his present field of practice.

2. Postgraduate medical education, as defined in this report, should not attempt to qualify a physician for entering a specialized field of practice.

3. Postgraduate medical education divides itself into two independent categories which should be clearly differentiated; namely,

(*a*) Instruction for general practitioners.

(*b*) Instruction for those who are already qualified as specialists.

4. Postgraduate medical education should be offered only by those who are qualified to provide satisfactory instruction.

5. Postgraduate medical education should be coordinated by existing agencies in each state that are concerned with the health and medical care of the population.

This report has been criticized primarily because of its point of view. It has been charged that it represents a concept that the family doctor is merely an agent to direct his patient to a specialist. Today most of the physicians of the United States are in general practice. Unfortunately that very fact makes them less prominent in the groups of physicians who concern themselves with committees, councils and similar bodies that spend much of their time in discussions of medical education. The *Journal of the Michigan State Medical Society* has urged that a commission of general practitioners be organized to establish their point of view as to the principles which should underlie the training of interns. Some hospitals are beginning to recognize the validity of this criticism by the appointment of general practitioners to membership on their staffs and also by the establishment of residencies in general practice. Graduate medical education is still in what might be called an early experimental stage. Fortunately, this fact is recognized by most of the bodies which are concerned in the field and even the standards set by the certifying boards are not yet to be considered as the ultimate in each of these fields. The contribution of the Commission on Graduate Medical Education may be classified as "work in progress." The conditions change so rapidly that most of the tabular data which make up the appendix are already obsolete.

Allergiya i desensibilizatsiya. Pod redaktsiey D. E. Alperna. L'allergie et la désensibilisation. Cloth. Price, 11 rubles. Pp. 217, with illustrations. Kharkov: Izdanie Ukrainskogo Instituta Eksperimentalnoy Meditsiny, 1940.

This small volume, published by the Ukrainian Institute of Experimental Medicine, contains brief reports on experimental and clinical studies in allergy and desensitization by Prof. D. E. Alpern and his co-workers. Alpern makes a distinction between specific and nonspecific desensitization. The first consists in creating within the organism a resistance to the antigen by immunobiologic action in the presence of antibodies. By nonspecific desensitization is meant the reduction of the exaggerated reactivity by means other than immunobiologic, namely, through the intervention of the regulatory systems of the organism, its metabolism and so on. There are chapters dealing with animal experiments and clinical trial of histamine, of ultrashort waves and of intermedin. Alpern claims to have obtained this hormone containing extract of the pars intermedia of the hypophysis long before Zondek (1932) described intermedin containing the melanoforming hormone. He describes his method of obtaining the hormone from the hypophysis of small and large horned cattle. Several chapters are devoted to the effect of intermedin. Its effectiveness is determined by the extent to which allergy participates in a given pathologic state. The greater the allergic factor, the more effective is the intermedin. The latter was always effective in shock attending blood transfusion, in allergic disorders of the nasal mucous membranes, in phlyctenules, in recurrent rheumatism and in other allergic diseases. The work is in Russian with a synopsis in French accompanying each chapter.

Progress in Medicine: A Critical Review of the Last Hundred Years. By Iago Galdston, M.D. With a foreword by Henry E. Sigerist, M.D. Cloth. Price, $3. Pp. 347. New York & London: Alfred A. Knopf, 1940.

Interesting himself in philosophies more than in events and personalities, the author has produced here a historical meditation concerning medical progress ostensibly only in the last century but in reality covering much more in point of time. His approach is reminiscent of Singer rather than of Clendening, Haggard or Major, whose historical essays for lay readers bid fair to become lasting contributions to this field of medical literature. He objects to "history viewed in the light of its heroes" because the lapses between the times of heroic individual achievements appear to be dark ages or voids. "History viewed as the progression of ideas has no dark ages" the author says in his introduction.

Proceeding on this theory, he opens with a review of "Preludes to Pasteur." Tracing the evolution of man's conceptions as to the causes of disease from Homer's description of the plague of the mules and the swift dogs which was ultimately communicated to man and attributed to the displeasure of Phoebus Apollo with Agamemnon, he sketches swiftly the outlines of development to the era of Pasteur, Koch and their compatriots and followers, with emphasis on the flow of thought and the growth of ideas and understanding rather than on the men through whom the ideas are implemented. As he states in his introduction "Ideas . . . do not progress by themselves. They have need for vehicles, human beings. We never confront a disembodied idea. There is always a man to express it, to cherish it, to defend it, to propagate it. In that respect ideas and human life have this in common, that each man receives his from another, to pass on, better or worse, but never to create independently."

From the pre-Pasteur era he traces the progress of medical thought through the era of those whom he calls the pasteurians, whose thinking was along microbian lines, to the challenge of nutrition problems, the rise of glandular knowledge, mental hygiene and psychiatry from Mesmer to Freud, a century of clinical progress, and a closing chapter entitled "Whither Medicine?" This is a prognosis for medicine in the scientific, not the economic, realm. The author's forecast is perhaps best represented, as far as brief quotations can represent it, in the following passages: "It is none too optimistic to believe that during our very lifetime 'some great truth has been loosened' in medicine, a truth that holds the proper precinct of medicine to be life, not death, that deems its primary concern to be health

not disease, that looks to the safeguarding of the man rather than to the conquest of the malady." However, as to the imminence of achievement of this "loosened truth" he says "The time . . . is not ripe, though medicine is, for the widespread practice of personal preventive medicine. I say medicine is ripe, but its ripeness is not full blown. Medicine today is not only adding much to its knowledge but is summing up much of what it has gathered into larger concepts and broader understanding. . . . But we do have more parts to put together." His final summation is in the words of Cicero: "Man never come closer to the gods than in giving health to men."

The book is thoughtful and thought provoking. It is not light reading, yet it is not hard reading, thanks to the author's broad acquaintance with medical and cultural literature, his individuality of style and the richness of his vocabulary. It is heartily recommendable for the physician and the thoughtful lay reader.

Textbook of Public Health. By W. M. Frazer, O.B.E., M.D., Ch.B., Medical Officer of Health, City and Port of Liverpool, and C. O. Stallybrass, M.D., Ch.B., D.P.H., Deputy Medical Officer of Health, City and Port of Liverpool. (Formerly Hope and Stallybrass.) Tenth edition. Cloth. Price, $6.50. Pp. 504, with 64 illustrations. Baltimore: William Wood & Company, 1940.

The present edition of this standard work is thorough in all aspects of the subject and as complete a textbook on public health as the graduate student could desire. The obvious comparisons between the English and American methods are interesting, especially the section on milk production and inspection. Apparantly pasteurization is not nearly as widespread a procedure in the British Isles as it is in the United States. The chapters on industrial hygiene, water, sewage disposal and housing are progressive and represent the modern trend of thought. Health officers in the United States have much to learn from the planned housing programs of Britain, and the various pages devoted to proper dwellings are of value and importance. Of additional interest is the chapter pertaining to marine hygiene, a subject that is frequently neglected in the average book on public health. The chapter on meteorology perhaps overemphasizes the effects of climate. Maternity and child welfare and school medical service are minutely described, including plans and diagrams of child welfare clinics. The absence of a separate chapter on public health nursing might be considered a defect. A departure from the usual is noted in the chapter on hospital administration, an oft neglected part of public health administration. This excellent volume closes with a chapter on medical aspects of civil air defense which is timely and well written. The book is thoroughly indexed.

Clinical Urology. By Oswald Swinney Lowsley, A.B., M.D., F.A.C.S., Director of the Department of Urology (James Buchanan Brady Foundation) of the New York Hospital, New York, and Thomas Joseph Kirwin, M.A., M.S., M.D., Attending Surgeon of the Department of Urology (James Buchanan Brady Foundation) of the New York Hospital. Volumes I and II. Cloth. Price, $10, per set. Pp. 898; 899-1684, with 370 drawings by William P. Didusch. Baltimore: Williams & Wilkins Company, 1940.

In the development of this work, planned primarily for the medical student and general practitioner, the authors have followed classic arrangement by beginning with the general diagnostic procedures, including a chapter on history taking and physical examination, and then considering the organs of the urogenital tract in anatomic sequence from without inward. The first volume covers the external genitalia, with a special chapter on gonorrhea, and includes all the tissues through the prostate gland. The second volume is concerned with the bladder, the ureters and the kidneys, and there is a concluding chapter on radium and roentgen therapy of the genito-urinary tract.

Exceptional in this book are the magnificent illustrations by Didusch, of which there are a tremendous number both in black and white and in colors. Exceptional also is the readability of the type, which makes study of the book a veritable pleasure for the eye. The work is one of the most practical that is available, and the information particularly with regard to treatment is succinct and definite. The numerous side headings and center headings in various type make the acquiring of information relatively simple because the book falls naturally into excellent outline form. So rapidly has chemotherapy developed in recent years that the book is already a little behind times as far as concerns some of the newer sulfonamide derivatives. Indeed, the book includes an extraordinary spelling of sulfathiazole. Nevertheless the volume contains references to periodical literature as late as February 1939. As a guide to the general practitioner these volumes may be recommended for their practicality and for their well considered didactic expression.

Problemy teoreticheskoy i prakticheskoy meditsiny. Lektsii po usovershenstvovaniyu vrachey. Sbornik sedmoy. Otvetstvenny redaktor: S. Ya. Shumarov. [Problems of Theoretical and Practical Medicine. Postgraduate Lectures for Physicians. Seventh collection.] Boards. Price, 7 rubles. Pp. 272, with illustrations. Moscow: Izdanie Gosudarstvennogo Tsentralnogo Instituta Usovershenstvovaniya Vrachey, 1938.

This volume, in Russian, contains a series of lectures delivered in a ten day review course offered by the Central Postgraduate Institute. The ten day program was arranged so that each lecture presented a more or less complete review of the present status of a problem with emphasis on the contributions of Soviet medicine. The most prominent representatives of Soviet medicine were invited to participate. Preference was given to physiologic problems. On reading some of these lectures the reviewer felt that either the average Soviet doctor was head and shoulders above an average American physician or that the lectures went over their heads. They read in fact as an advanced seminar in physiology. Perusal of the titles alone is sufficient to indicate their highly theoretical nature. Thus, "The Modern Status of the Localization of Nervous Functions," "The Problem of the Center and the Periphery in the Physiology of Nervous Activity," "The Cortex and the Work of Internal Organs," "Chemical Nature of Ferments."

The Chinese Way in Medicine. By Edward H. Hume. Cloth. Price, $2.25. Pp. 189, with 9 illustrations. Baltimore: The Johns Hopkins Press, 1940.

This book falls into three parts. The first deals with the universe and man in Chinese medicine and is a summary of the views of Chinese philosophers whose teachings afford the philosophical basis for Chinese medical procedures. These include the cosmic philosophy of Lao-tse with its two opposed forces, Yin, the negative, or female, and Yang, the positive, or male; the kwei or animal spirit, and the shen or intellectual spirit, both acquired during fetal life from the parents. Childbirth is a period of great susceptibility to spirits, and mental disturbances are due to excitement of the shen; hence exorcism by the cock, whose kinship with the sun confers on the blood of that bird subtile powers over the mind. The vegetable kingdom is also beset by spirits. The pine, cypress, peach and fungi possess the magic ling. Tao, the Way of Nature, gave rise to the belief in immortality, the Happy Islands, and indirectly to the elaborate systems of breathing, diet and physical exercises conducive to longevity. The mineral world also had its place in Chinese medicine, and gold, jade and pearls their place in medical lore. The second part is devoted to a review of the medical classics of the Chinese, in which are traced the rise of the elaborate use of the pulse in diagnosis, the development of herbals, the elaboration of anesthesia and surgical practice, and vaccination. The third part enumerates the distinctive contribution from Chinese medicine. The animistic, cosmic and medicamental approach to disease are interesting historically but the last is most fruitful. Their empiric methods led to the use of the lining of the pig's stomach in anemia, the use of marine algae in thyroid disease, and of fish livers in scrofula and lung diseases. The use of poisonous reptiles and of the pills of eight poisons belong with that of the cicada and of jade more in the field of magic than of medicine. The important contributions are the origin of medical libraries and of medical monographs such as those on leprosy, venereal disease, smallpox, beriberi, obstetrics, gynecology and ophthalmology. Among medicaments of proved value used in Chinese medicine are stramonium, deer's horn (for calcium), Ephedra vulgaris, musk, iodine from seaweed, toad venom, chaulmoogra oil, tang kwei from Cryptotaenia canadensis, from which eumenol is derived, anthelmintics, fish oils and arsenic. Physical therapy is found in acupuncture and moxa, in the art of breathing and in physical exercises.

Mosquito Control: Practical Methods for Abatement of Disease Vectors and Pests. By William Brodbeck Herms, Sc.D., and Harold Farnsworth Gray, Dr.P.H. Cloth. Price, $3.50. Pp. 317, with 60 illustrations. New York: Commonwealth Fund; London: Oxford University Press, 1940.

This handy book on mosquito control is an exhaustive study of the principles underlying the problem and the actual methods of abatement. Beginning in the introduction with a brief historical sketch of the origin of control, the work continues with the brief discussion of the cost of malaria from an economic point of view. State laws are reviewed and various nonofficial agencies for mosquito abatement are described. The various methods of control are described in great detail, as is also their adaptation to various types of land to be treated. An interesting chapter written with a sense of dry humor rarely seen in scientific textbooks is that on mosquito control by use of fish. The special features of the problem in urban and rural areas are described and the problem of the mosquito in the airplane and the military phases are not neglected. Considerable emphasis is placed on the education of the public in order to maintain interest and support for the carrying on of the work. Appendixes, dealing with the distribution of the anophelines and their larval habitats and a classification of methods, together with a selected bibliography, make it an extremely handy reference book. The authors have been actively associated with mosquito control work on the west coast for thirty years and the book will serve as a valuable guide for all those engaged in any aspect of mosquito abatement.

Synopsis of the Principles of Surgery. By Jacob K. Berman, A.B., M.D., F.A.C.S., Assistant Professor of Surgery, Indiana University School of Medicine, Indianapolis. Fabrikoid. Price, $5. Pp. 615, with 274 illustrations. St. Louis: C. V. Mosby Company, 1940.

As the title indicates, this is another synopsis of the principles of surgery. Yet this one is much different from all the others on the subject and is probably the best that has been the privilege of the reviewer to see. The essential and most valuable feature of the book is that it is written with the idea of correlating the basic sciences with the fundamental principles of surgery. This the author accomplishes in a novel manner. The body of the text contains a discussion of the standard principles of surgery which are found in almost every textbook, while in footnotes, nearly as extensive as the text itself, he covers the related and pertinent facts of anatomy, pathology, biochemistry and physiology. Though the discussions are necessarily brief, the subject matter is covered completely and well. There is a tremendous amount of information between the covers of this volume, all of which is abreast of the time. The book is written in clear, simple style. It is attractively printed and contains a large number of excellently reproduced photographs and line drawings which enhance the value of the text. The book is highly recommended for surgeons as well as students for whom it was intended.

Clinical Dental Roentgenology: Technic and Interpretation Including Roentgen Studies of the Child and Young Adult. By John Opple McCall, D.D.S., F.A.C.D., Director, the Murry and Leonie Guggenheim Dental Clinic, New York, and Samuel Stanley Wald, D.D.S., F.A.C.D., Head of the Department of Diagnosis and Roentgenology, the Murry and Leonie Guggenheim Dental Clinic and School for Dental Hygienists. Cloth. Price, $5.50. Pp. 319, with 1,046 illustrations. Philadelphia & London: W. B. Saunders Company, 1940.

This book is by teachers of dentistry, intended for practicing dentists and for radiologists or other physicians interested in dental roentgenology. The pages on technic call for clarification and condensation and chapter II, on electricity and roentgenology, merits no serious consideration by readers; but the bulk of the work, which deals with diagnosis, is excellent and is recommended without reservation to physicians desirous of improving and modernizing their ability to interpret dental roentgenograms. The anatomy of the teeth and jaws at all ages from fetal to adult life is described, and certain concepts of development that have become established among orthodontists are convincingly disputed. Periapical lesions, unerupted teeth, salivary duct stones and infections, tumors and injuries of the jaws are well described and illustrated. In addition to these familiar subjects there are discussed many others not so well known to physicians, such as growth phenomena, dental caries and periodontal disease.

Miscellany

PROPOSED ADDITIONS AND DELETIONS FOR THE UNITED STATES PHARMACOPEIA

Herewith is the report of the Subcommittee on Scope of the U. S. Pharmacopeia, Twelfth Revision. It consists of (*a*) a list of articles not formerly described in the Pharmacopeia but now recommended for inclusion in the U. S. P. XII and (*b*) a list of articles official in the U. S. P. XI but not recommended for admission to U. S. P. XII (commonly spoken of as "deletions").

ARTICLES NOT FORMERLY PHARMACOPEIAL NOW RECOMMENDED FOR THE U. S. P. XII

Absorbent Gauze
Absorbent Gauze, Sterile
Adhesive Absorbent Compress
Antipneumococcus Serum (the new monograph to cover all types)
Calaminae Preparata
Calcium Mandelate
Dextrose Solution (for injection 50 per cent)
Dextrose (50 per cent) and Sodium Chloride (30 per cent) Solution (for injection)
Elixir Cardamomii Compositum
Elixir Iso-Alcoholicum
Elixir Phenobarbitali
Elixir Terpini Hydratis
Ethyl Carbamate
Gas Gangrene Antitoxin (to include types now used)
Gauze Bandage
Glycocoll (Amino Acetic Acid)
Immune Serum for Scarlet Fever, Human
Immune Serum for Measles, Human
Immune Globulin (Placenta Extract) Human
Lotio Calaminae
Lotio Calaminae Phenolata (2 per cent Phenol)
Magnesium Trisilicate
Oleum Hippoglossi (Halibut)
Ouabain
Picrotoxin
Picrotoxin Solution (for injection)
Potassii Chloridum
Quinine Hydrochloride
Quinine Hydrochloride with Ethyl Carbamate Solution (for injection)
Riboflavin
Ringer's Solution
Serums, Dry and Liquid forms authorized for all U. S. P. Serums
Surgical Silk and other Surgical Sutures
Surgical Silk and other Surgical Sutures Sterilized
Syrupus Ammonii Mandelatis
Syrupus Glycyrrhizae
Syrupus Rubi Ideaei
Tabellae Aminopyrinae
Tetanus Toxoid
Tetrachloroethylene
Theobromine with Sodium Acetate
Totaquinine
Transfusion Normal Plasma, Human
Transfusion Normal Syrum, Human
Trichloroethylene
Urea
Vitamins A and D in Oil (Cod Liver Oil Strength)
Zinc Peroxide

The following additional items, needed as "pharmaceutic necessities," must be added as new admissions:

Compound Spirit of Cardamom
Cudbear
Oil of Caraway
Oil of Cardamom
Raspberry Juice
Spirit of Bitter Almond
Tincture of Cudbear

ARTICLES OFFICIAL IN THE U. S. P. XI, BUT NOT ADMITTED TO THE U. S. P. XII, COMMONLY SPOKEN OF AS "DELETIONS"

Acetum Scillae
Acidum Aceticum Dilutum
Acidum Acetyltannicum
Acidum Sulfuricum Aromaticum
Aconitum
Albumini Tannas
Ammonii Benzoas
Ammonii Bromidum
Ammonii Salicylas
Arseni Triiodidum
Asafoetida
Bismuthi Subgallas
Calcii Bromidum
Calcii Creosotas
Cannabis
Cantharis
Capsicum
Carbo Activatus
Carbromalum
Ceratum Cantharidis
Cinchona
Colchici Semen
Copaiba
Creosoti Carbonas
Creosotum
Dichloramina-T
Emplastrum Cantharidis
Emulsum Asafoetidae
Extractum Cannabis
Extractum Nucis Vomicae
Ferrum
Fluidextractum Belladonnae Radicis
Fluidextractum Cannabis
Galla
Guaiacol
Hydrargyri Iodidum Flavum
Iodoformum
Kino
Liquor Ammonii Acetatis
Liquor Ferri Chloridi
Liquor Ferri Tersulfatis
Magma Ferri Hydroxidi
Massa Hydrargyri
Merbaphenum
Mistura Opii et Glycyrrhizae Composita
Oleum Santali
Pancreatinum
Paraffinum
Pepsinum
Pilocarpinae Nitras
Pilulae Aloes
Podophyllum
Potassii Chloras
Pulvis Ipecacuanhae et Opii
Pulvis Sennae Compositus
Pyrogallol
Quinina
Resina Podophylli
Santoninum
Scilla
Serpentaria
Sodii Acetas
Spiritus Aethylis Nitritis
Spiritus Chloroformi
Strychninae Nitras
Sulfonethylmethanum
Sulfur Lotum
Syrupus Ferri Iodidi
Syrupus Scillae
Terebenum
Theobromina cum Sodii Salicylate
Tinctura Aconiti
Tinctura Cantharidis
Tinctura Capsici
Tinctura Cinchonae Composita
Tinctura Colchici Seminis
Tinctura Ferri Chloridi
Tinctura Kino
Tinctura Scillae
Tinctura Valerianae
Tinctura Veratri Viridis
Unguentum Gallae
Valeriana
Veratrum Viride

Physicians are encouraged to send comments on the foregoing proposals either to the Chairman of the Pharmacopeia Revision Committee, Dr. E. Fullerton Cook, Forty-Third Street and Woodland Avenue, Philadelphia, or to the Editor of THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION.

Bureau of Legal Medicine and Legislation

MEDICOLEGAL ABSTRACTS

Basic Science Law (Arkansas): Constitutionality and Applicability to Chiropractors.—The legislature of Arkansas in 1915 enacted a statute creating a state board of chiropractic examiners and required it to examine prospective chiropractors in the subjects of anatomy, physiology, symptomatology, chemistry, hygiene, chiropractic principles and diagnosis. In 1929 a basic science law was enacted in Arkansas which requires every applicant desiring a license to practice the healing art or any branch thereof to pass an examination in the basic sciences—anatomy, physiology, chemistry, bacteriology and pathology—and present to the licensing agency a certificate to that effect, issued by the state board of examiners in the basic sciences, before he may be permitted to take a further examination for the particular branch of the healing art which he desires to pursue. This law excepted from its application dentists, nurses, midwives, optometrists, chiropodists, barbers, cosmeticians and Christian scientists. By reason of these statutory provisions, the plaintiff, the Arkansas Medical Society, petitioned the Pulaski chancery court for an injunction (1) to restrain the defendant state board of chiropractic examiners from issuing licenses to practice chiropractic to any applicants who failed to present certificates showing satisfactory completion of the required examination in the basic sciences and (2) to enjoin two individual chiropractors from practicing chiropractic under invalid licenses issued to them by the state board of chiropractic examiners without their having complied with the basic science law. From an order of the court denying the petition, the plaintiff appealed to the Supreme Court of Arkansas.

The defendants contended that the basic science law does not apply to the practice of or the licensing to practice chiropractic and that so far as it attempts to regulate such licensing or practice it constitutes an unreasonable and unconstitutional interference with the right to practice chiropractic. In support of this contention the defendants argued that bacteriology and pathology, two of the subjects in which applicants for licensure to practice the healing art are required by the basic science law to take examinations, were neither essential to nor connected with the practice of chiropractic. With this contention, however, the Supreme Court of Arkansas could not agree. The legislature, said the court, believed it proper that all persons seeking a license to practice the healing art should have a knowledge of, among other subjects, bacteriology and pathology, and we cannot say their inclusion as to chiropractic was unreasonable, arbitrary and without any relation to such practice. Bacteriology is defined by Webster as "The science which deals with the study of bacteria. It is a branch of botany, but some of its most important practical relations are with hygiene, medicine and agriculture." Certainly bacteriology has some relation to the practice of chiropractic since "some of its most important practical relations are with hygiene," a subject in which a prospective chiropractor is required by the chiropractic practice act to take an examination. Pathology is defined as "The science treating of diseases, their essential nature, causes and development, and the structural and functional changes produced by them." In reply to the defendants' argument that the subject of pathology was not related to the practice of chiropractic because chiropractors do not diagnose or treat disease but merely locate "the nerve pressure of the spinal column" and make proper adjustments to relieve that pressure, the court said: "If he does not treat diseases, what does he treat? Does he manipulate the vertebrae of a well person just for the pleasure of such well person? There would be no excuse for any regulatory chiropractic laws, if they were not engaged in treating disease." In the judgment of the court, the basic science law does apply to the practice of and the licensing to practice chiropractic, which is a branch of the practice of the healing art, and applicants for license must successfully pass examinations in the basic sciences before the basic science board of examiners as a prerequisite to eligibility for examination before the chiropractic board.

Furthermore, continued the court, the basic science law does not abridge the rights and privileges of chiropractors but simply places additional requirements on the qualifications for practice. It merely regulates the practice of chiropractic but does not ban it. The fact that the basic science law excepts from its operation dentists and certain others does not constitute, as the defendants claimed, an arbitrary and unreasonable classification.

The Supreme Court of Arkansas concluded that the basic science law is constitutional, and so it reversed the judgment and remanded the case with directions that the injunction be granted. An appeal to the United States Supreme Court was dismissed for want of a substantial federal question.—*Stroud et al. v. Crow et al. (Ark.), 136 S. W. (2d) 1025; 61 Sup. Ct. 17.*

Society Proceedings

COMING MEETINGS

American Association for the Study of Neoplastic Diseases, Baltimore, Dec. 19-21. Dr. Eugene R. Whitmore, 2139 Wyoming Ave. N.W., Washington, D. C., Secretary.

American Student Health Association, Ann Arbor, Mich., Dec. 27-28. Dr. Ralph I. Canuteson, University of Kansas, Lawrence, Kan., Secretary.

Annual Congress on Industrial Health, Chicago, Jan. 13-15. Dr. Carl M. Peterson, 535 N. Dearborn St., Chicago, Secretary.

Eastern Section, American Laryngological, Rhinological and Otological Society, Philadelphia, Jan. 10. Dr. N. S. Weinberger, Robert Packer Hospital, Sayre, Pa., Chairman.

Middle Section, American Laryngological, Rhinological and Otological Society, Chicago, Jan. 27. Dr. Walter H. Theobald, 307 North Michigan Blvd., Chicago, Chairman.

Society of American Bacteriologists, St. Louis, Dec. 27-29. Dr. I. L. Baldwin, Agricultural Hall, University of Wisconsin, Madison, Wis., Secretary.

Southern Section, American Laryngological, Rhinological and Otological Society, Nashville, Tenn., Jan. 8. Dr. William G. Kennon, Doctors Bldg., Nashville, Tenn., Chairman.

Western Section, American Laryngological, Rhinological and Otological Society, San Francisco, Feb. 1-2. Dr. Robert C. Martin, 384 Post St., San Francisco, Chairman.

THE AMERICAN RHEUMATISM ASSOCIATION

Seventh Annual Meeting, held in New York, June 10, 1940

DR. LORING T. SWAIM, Boston, Secretary

(Continued from page 2026)

The Familial Epidemiology of Rheumatic Fever

DR. MAY G. WILSON, DR. RALPH E. WHEELER, and MORTON D. SCHWEITZER, PH.D., New York: Taking the family as the unit for epidemiologic study, the relation of environment, contagion and heredity to the spread of rheumatic fever in 112 families was considered. It was found that the frequency of rheumatic fever did not differ significantly in families of varying economic levels ranging from dire poverty to middle class comfort, although rheumatic recurrences were less frequent among children living under relatively favorable environmental conditions. No evidence was obtained that rheumatic fever is passed back and forth from case to case in the family. Simultaneous attacks in the household were no more frequent than might have been expected from chance association. The incidence of recurrences bore no direct relation to the size of family or the number of rheumatic members and seemed to represent recrudescences of existing disease rather than new infections. Unlike most acute communicable diseases, the age of onset for children presumably exposed within the family (secondary cases) was not earlier than for those exposed "outside" the family (primary cases). No evidence was obtained to indicate that a rheumatic parent or child constituted a hazard per se to the nonrheumatic or quiescent members of the family group. Two different secondary attack rates were obtained. The rate for families in which one parent was rheumatic was double that for families in which

neither parent was rheumatic and four times as great in families in which both parents were rheumatic. These observations are apparently inconsistent with a hypothesis of contagion. They do, however, afford additional evidence that hereditary susceptibility underlies the familial incidence of rheumatic fever.

DISCUSSION

DR. HELEN B. TAUSSIG, Baltimore: Our studies in Baltimore fundamentally support those of the authors. My associates and I have found that there is a high familial incidence in rheumatic fever and there is evidence of a strong hereditary factor. We too have shown that its behavior is not that of an acute communicable disease. Its development is more like that of tuberculosis than like measles. We agree entirely that the incidence of rheumatic fever is higher in families in which one or both parents has had rheumatic fever than when neither parent has had the disease. On the other hand, I do not think this can be taken as evidence that the disease is primarily due to a hereditary predisposition and not an environmental factor. That belief rests on the assumption that chronic rheumatic fever is not contagious; we have no evidence to support that view. On the contrary, the fact that most people with rheumatic heart disease die of the disease leads to the belief that infection persists for a long time and may play an important part in the spread of the disease. It is noteworthy that after introduction of an acute case of rheumatic fever the secondary attack rate doubles and increases proportionately as much in the group in which the parents have not had rheumatic fever as in the group in which the disease is present in one or both parents. This, we believe, is evidence that this is an environmental factor. We have no indication whether the environmental factor is nutritional or exposure to damp and cold, but we do believe that there is an environmental factor as well as a hereditary one.

DR. JOHN R. PAUL, New Haven, Conn.: This discussion is concerned with the nature of rheumatic fever. More knowledge of this particular aspect of this disease is what we need. Dr. Wilson and her co-workers have used a difficult technic, but it is a method which holds some promise in the study of this and other diseases. It was used with success by Dr. Opie in tracing the spread of tuberculosis through families. The advantage, as the authors expressed it, which students of tuberculous families have over those who study rheumatic fever is that in tuberculosis there are many more diagnostic aids. One difficulty with rheumatic fever families is that of trying to discover what is really going on. The results in our family studies do not differ much from those that Dr. Wilson has shown, but our conclusions are, perhaps, not quite as definite. My associates and I believe that heredity plays an important, though not necessarily a dominant, part in determining the prevalence of this disease. We believe that there seems to be adequate evidence to show that the children of rheumatic parents acquire this disease with greater frequency than do the children of nonrheumatic parents. The degree to which hereditary influences prevail in rendering the host more or less susceptible to many infectious diseases is the question. Of course there must be strong environmental influences at work, such as climate, and poor living conditions. Another example of the effect of environment in rheumatic families is the manner in which upper respiratory infections precipitate an attack of rheumatic fever. Acute epidemics of rheumatic fever occur when an acute infection invades a "rheumatic family" just as they occur when such infections invade a convalescent home.

DR. JAMES F. RINEHART, San Francisco: The authors speak of a group in which the food was adequate and a group in which it was not adequate. I should like to ask to what extent a detailed analysis of nutrition was made. I am thinking of a possible deficiency in vitamin C.

DR. T. DUCKETT JONES, Boston: I should like to ask whether the authors have had any experience with offspring of rheumatic parents, either one or both, who have lived entirely away from the environment of the parents, even in different sections of the country, and especially where rheumatic fever is not common.

DR. MAY G. WILSON, New York: The data have not all been presented because of time limitations. We had 800 calendar years of activity, of which 25 per cent were simultaneous years, that is multiple cases of activity during the same year. This is no more than might be expected by chance. The work reported by the Johns Hopkins group on the prefamilial and postfamilial attack rate is still a subject of debate between us. In these 112 families the children were not separated, but we know of families in our clinic in which children living apart from parents had rheumatic fever. I think data might be included on children who are adopted or sent out to other homes where there are nonrheumatic parents. I have asked those engaged in adoption work to look out for it. Such data would be significant. These homes have been under long observation of our social workers who were familiar with the food served to the children. Notes were made at each home visit as to the amount and balance of food, and particularly if vitamin C was inadequate.

Cultural Studies on Rheumatoid Arthritis and Rheumatic Fever

DRS. D. MURRAY ANGEVINE, SIDNEY ROTHBARD, and RUSSELL L. CECIL, New York: The patients with rheumatoid arthritis studied were those in the active stage of the disease, that is with pain and swelling of the joints and usually an increase in the sedimentation rate. The blood cultures were taken whenever possible in a dust-free, airfiltered room. Masks were worn by the operators during all procedures, and the transfers of cultures were made with rubber bulbs on the pipets. The aerobic clot method was used for most cultures. The principal medium used was dextrose phosphate broth. Repeated subcultures were made at intervals of five days for one month. Forty-nine of sixty-one (80 per cent) blood cultures made on fifty-eight patients yielded no growth. The following organisms were obtained from twelve of the cultures: Five showed a large gram-positive diplococcus (not identified), four Staphylococcus albus and the others an alpha prime streptococcus, Staphylococcus aureus and B. subtilis respectively. Additional cultures were made of synovial fluid and tissue, as well as subcutaneous nodules on similar medium enriched with horse blood. Twenty-two cultures of synovial fluid from twenty patients were sterile. Five of seven cultures of synovial tissue were sterile; Micrococcus tetragenes was grown in one instance and Staphylococcus albus in one. Five of nine subcutaneous nodules were sterile, three yielded Staphylococcus albus and one a gram-positive diplococcus. Special cultural studies were made according to the method of Klieneberger for the presence of a pleuropneumonia-like organism in the synovial fluid, synovial tissue or subcutaneous nodules from thirteen patients with rheumatoid arthritis. In no instance was such an organism recovered. The synovial fluid, tissue, or subcutaneous nodules from sixteen patients were inoculated on the chorio-allantoic membrane of the chick embryo, 185 eggs being inoculated and thirty-five subpassages made. No significant transmissible lesion was produced. Similar material was also instilled into the nares of young white mice (strain CF 1) under light ether anesthesia. Occasionally small areas of pneumonia developed after the first instillation. Thirteen of 127 mice injected in this manner developed small, patchy areas of pneumonia following the first instillation. Several passages, usually six, of normal and pneumonic lungs were made at intervals of from four to six days. In a few instances a transmissible pneumonia developed; however, this was so irregular and inconsistent that we feel it was probably caused by a mouse virus or pleuropneumonia-like organisms. Material from seven cases of rheumatoid arthritis was injected intravenously, intracerebrally, intraperitoneally or subcutaneously into mice. No significant lesions were produced, nor was any transmissible agent recovered. Irradiated mice were used in many instances; however, no difference was found between these and the nonirradiated mice in respect to the development of pneumonia.

Tissues or exudates from eleven clinical cases of rheumatic fever and from eleven cases at necropsy were studied. The following were cultured for pleuropneumonia-like organisms: synovial fluid four, pleural exudate three, pharyngeal washings four and heart valves with verrucous vegetations, pericardium or myocardium obtained at autopsy five. Similar material preserved by freezing from eleven of the cases was also cultured. In no instance were pleuropneumonia-like organisms recovered. The pleural fluid from one, and the synovial fluid from four

clinical cases, as well as tissue from three hearts obtained at autopsy, were inoculated onto the chorio-allantoic membrane and passed at intervals. No significant transmissible lesion was produced. Material from nine of the clinical cases and seven of the autopsies was instilled into the lungs of 145 mice and passages were made as previously described. In all, 486 mice were used. Sixty-seven mice were inoculated by other routes with material from two clinical cases and four autopsies. The results of these studies were similar to those described for rheumatoid arthritis.

Extensive cultural studies have been made in eighty-three cases of rheumatoid arthritis and twenty-two cases of rheumatic fever. No organism of significance has been consistently isolated.

DISCUSSION

DR. M. HENRY DAWSON, New York: Only one conclusion seems possible: if bacteria actually are present in the blood and joint tissues of patients suffering from rheumatoid arthritis they must exist in some form which cannot be detected by present day bacteriologic methods. Collier in Batavia, Java, has reported the occurrence of a spontaneous polyarthritis in rats. Cultures on the affected joints have been negative but the disease is readily transmitted from animal to animal. Findlay and his associates have described a similar disease in rats from which they have isolated a pleuropneumonia-like organism or "L form." I have had the opportunity of studying Collier's rats and have come to the conclusion that the disease is quite different from rheumatoid arthritis. Another interesting study has recently been reported by Collins on arthritis in swine. This disease is due to the organism Erysipelothrix rhusiopathiae and bears a closer relationship to the human disease. However, it is by no means clear that arthritis of swine bears any relationship to rheumatoid arthritis.

DR. HOMER F. SWIFT, New York: Dr. Brown and I made a preliminary report on the possible recovery of pleuropneumonia-like micro-organisms from rheumatic patients. We have now established that these micro-organisms probably originated from the mice inoculated with the exudates and have been unable to grow these germs directly from the exudates or tissues of patients with rheumatic fever. The technics have been so well developed that these negative results are significant. In animal inoculations Dr. Angevine and his co-workers used one strain of mice, of which about 10 per cent developed pneumonia. My associates and I employed another strain and obtained a much higher percentage of pneumonia, from which numerous pleuropneumonia-like micro-organisms were easily recovered when the pneumonic lung was rubbed over 30 per cent ascitic fluid agar and the plates were examined microscopically after from two to four days' incubation. In our studies mice inoculated with rheumatic exudates had a much higher proportion of pneumonia than did controls inoculated with nonrheumatic exudates. This suggests that possibly the rheumatic exudates contained aggressin-like substances that made the pleuropneumonia-like micro-organisms carried by the mice in their upper respiratory tracts become more pathogenic; for, confirming Dr. Albert Sabin's studies, we have found that many of these mice carry in their conjunctivas these peculiar micro-organisms.

In reviewing the history of bacteriologic studies in rheumatism the question arises Whence came the bacteria that have been reported as having been obtained? Outstanding among the various possible sources is the environment under which the cultures were made. Dr. Angevine's precautions in providing an atmosphere with little liability of contamination from air or other extraneous sources were important. In New York, at least, many positive cultures reported previously were made in Bellevue Hospital; and we know that in the old Bellevue Hospital it was difficult to find a good atmosphere, bacteriologically speaking. Before the advent of the automobile truck, horse manure was a prolific source of many streptococci in the air. Recently it has been shown that hemolytic streptococci are readily disseminated in the atmosphere of wards in which patients with scarlet fever or tonsillitis are treated.

Next arises the question of the significance of micro-organisms grown directly from blood cultures. When a tooth is pulled or tonsils are excised there is a certain period when bacteria, often streptococci, actually circulate in the blood. In a patient with a sore throat it is conceivable that there is a period when streptococci break through the natural barriers into the blood stream. Obviously in the etiology of subacute bacterial endocarditis the agents infecting the heart valves must be bacteria carried originally by the blood. As already mentioned, when animals are employed to recover micro-organisms from a patient the difficulty always arises of determining whether the germs found are from the animal or patient. It should be indicated that the studies of Dr. Cecil and his collaborators have resulted in significant positive results. A few years ago when they were recovering streptococci from patients at Bellevue Hospital, he agreed to perform a blindfold test. The materials to be tested came from Presbyterian or Rockefeller Hospital and were sent to Dr. Cecil, who attempted to differentiate the rheumatic conditions in the patients from whom they came and made the correct diagnosis in many cases; but the differential feature was the agglutination by the serum of patients with rheumatoid arthritis of streptococci he had isolated from certain patients, and the absence of these agglutinins from the serum of patients with degenerative arthritis. Thus was discovered a test which many observers consider quite important. Lastly the discovery of the ability of pleuropneumonia-like micro-organisms to induce arthritis in mice and rats has led to a study of the beneficial action of gold salts in arthritis of these animals; and this type of experimental arthritis can be used to test the relative efficacy of various gold salts. I believe it has also been shown that other types of infectious arthritis in mice can be favorably influenced by these therapeutic agents. Thus, while the story is not finished, it still points to the value of experiments of this nature. Out of them progress is made toward an eventual solution of the mystery of arthritis.

DR. RUSSELL L. CECIL, New York: This is a negative report that seems to clear up a good many points. The studies of Drs. Nicholls and Stainsby were done at Bellevue Hospital; however, they were done in a sterilized room with great care and precaution. We were skeptical of these streptococci from the first. I think we were misled by the discovery of specific agglutinins in the patient's blood. Where did these streptococci come from? Dr. Nicholls and I often speculated about it when doubt was raised as to the accuracy of the work. The late Dr. Park thought the streptococci were actually in the blood but questioned their significance. We now think the pipets were the most likely source of contamination, rather than the air, since hemolytic streptococci are not common contaminants in air or on the skin. We think that, in spite of the cotton plugs in the sterile pipets, possibly some streptococci from the operator's mouth were blown through the pipets and introduced into the culture medium. This seems about as plausible an explanation as any. It would be difficult to set out deliberately and get 50 per cent contamination with streptococci in cultures. Bacilli of various kinds are common but it is unusual to get so many streptococci. The study of Dr. Angevine and Dr. Rothbard does not look pretentious but the number of animals used and the number of cultures made represent a great amount of work. As Dr. Swift said, this negative study means a really positive contribution to the subject. From my standpoint this report is in the nature of a retraction. I hope that a few years from now I shall not have to retract the retraction. I do not think that is likely.

DR. JOHN W. GRAY, Newark, N. J.: I am interested in the almost total lack of positive blood cultures in this report. One would normally expect a higher percentage from complicating acute upper respiratory infection alone, and if such cases were excluded from these studies the results might be of significance. Dr. Angevine and his collaborators made some cultures on my patients at the Hospital of St. Barnabas in Newark, and these patients had received sufficient treatment so that the disease became more or less quiescent. I have observed that positive cultures are seldom obtained during the summer months and that the largest number is found during the winter and spring months, when exacerbations of the disease following acute upper respiratory infections are most common. Whatever the cause of bacteremia may be, the presence of bacteria in the blood stream does not prove the microbic etiology of rheumatoid arthritis, nor does the absence of bacteria disprove it. I like Dr. Hench's conclusions regarding the infectious etiology of this disease when he

stated that as an investigator he must conclude that the evidence for infection, although impressive, is incomplete, but as a practicing physician he could not wait until evidence is complete and must commit himself, with reservations, to the microbic theory.

DR. R. H. FREYBERG, Ann Arbor, Mich.: About a year ago I became interested in the possible relationship between pleuropneumonia infection and the various rheumatic diseases, especially rheumatoid arthritis. With the assistance of Dr. Bauer and his associates, Dr. Dawson and others, I set about attempting to obtain cultures of pleuropneumonia-like organisms from synovial fluid, blood, subcutaneous nodules and the synovium itself of patients with rheumatoid arthritis primarily and of a few patients with rheumatic fever. All of the results have been entirely negative.

DR. J. ALBERT KEY, St. Louis: I had some negative results too in trying to obtain cultures of organisms from patients with rheumatoid arthritis, but changes which are practically identical with those found in rheumatoid arthritis can be produced in experimental animals by streptococci, although the polyarthritis which has been mentioned has not been produced. From the standpoint of the clinical course of the disease and from the standpoint of the pathologic changes that occurred in the tissues and also from the unexplained agglutination of streptococci which occurs in the blood of these patients I should regard this as an infectious disease. In spite of the sometimes positive, sometimes negative observations, statements and retractions, one may be prepared some day for Dr. Cecil to retract his retractions.

DR. CHARLES W. WAINWRIGHT, Baltimore: I should like to ask the authors concerning the status of the agglutination reaction in their cases of rheumatoid arthritis because this has been to my mind an important contribution in the study of this disease, provided they represent true agglutinins. There are many features about the reaction which point to true agglutinins and, on the other hand, features which indicate that it might be some curious physical-chemical phenomenon peculiar to this disease.

DR. T. DUCKETT JONES, Boston: During the past three or four years my associates and I isolated, according to the technic which Dr. Angevine described, a virus from the heart tissues of several patients with fatal rheumatic fever. The changes developing in the lungs of mice were interesting. The blood of the rheumatic fever patients neutralized this virus. The following year, however, we had less luck in isolating a virus from patients with fatal rheumatic fever. We tried not only cardiac but pulmonary tissues. To summarize, it soon became evident that the virus which was isolated was similar to the virus which can be isolated from patients with influenza. What this means we do not yet know. There are many other factors that come into play. The pleuropneumonia-like organisms and the question of mice viruses also enter the picture. We have isolated some which are similar to the noninfluenzal viruses recently described by Horsfal. Others isolated from stock mice behave much like the influenzal viruses. We now feel that we have isolated an influenza-like virus from rheumatic fever patients and from the respiratory tract rather than the heart. Whether it has any direct bearing on rheumatic fever it is impossible to say, but further studies of the presence of neutralizing antibodies in rheumatic fever patients may prove to be interesting.

DR. D. MURRAY ANGEVINE, New York: I should like to say something about the recovery of micro-organisms from the blood stream. One can take a blood culture on a pig at almost any time during twenty-four hours and recover organisms from the blood stream. Blood cultures can be taken from patients after a meal, and frequently organisms are recovered. If the blood of normal rabbits is repeatedly cultured, organisms may be recovered in perhaps 5 per cent of instances. In addition to the intrapulmonary route, we have injected mice intravenously, intracerebrally, intraperitoneally and into the foot pad. Dr. McEwen took cultures of the blood of various patients over a period of two years. It is of interest that in one year 20 per cent of the cultures were positive, whereas in the other year the incidence was much lower. I did not intend to mention the streptococcus agglutination reaction for we are still in a state of flux concerning it. When we began our work, a good many positive tests were obtained. However, as we have continued, there has been considerable variation in the results. During a period of four years, out of about 300 agglutination tests on definite cases of rheumatoid arthritis, our percentage of positives would be about 45. This is approximately the same figure as that reported by Dr. Bauer. Dr. Key suggests that we are getting away from the infectious theory of this disease. I may say that we have been continuously working along this line in animals. Two years ago in a report before this society, we showed pictures of what we thought were rather typical of the pathologic changes usually seen in rheumatoid arthritis. They showed lymph follicles produced by streptococci. So far we have not been able to obtain these lymph follicles in the synovia of any other animal except the rabbit.

Metabolism of Cartilage (Bovine) With Particular Reference to the Effects of Aging

DRS. OTTO ROSENTHAL, MORRIS A. BOWIE, and GEORGE WAGONER, Philadelphia: Cellular and metabolic studies have been made on bovine articular cartilage of varying ages. The cartilage from the older animals showed degenerative changes characteristic of hypertrophic arthritis. Microscopic examination and measurements of paraffin embedded slices of cartilage showed (*a*) the number of cells per cubic millimeter of tissue (cell content) declined with advancing age, and (*b*) the mean values of nuclear volume remained constant throughout the age groups.

The metabolic activity of surviving cartilage slices was determined by the method of Warburg. This activity was expressed as a ratio of metabolic rate to cell content. Glycolytic activity and the activity of the dehydrogenatic and oxygen-activating components of respiration were determined for cartilage of various ages. (*a*) Glycolytic activity remained essentially the same in all age groups. (*b*) Dehydrogenatic activity was determined from the oxygen uptake in the presence of methylene blue. It likewise remained essentially unaltered. The dye-stimulated respiration was accelerated by the addition of dextrose, succinate, lactate and pyruvate. This acceleration indicated that the cartilage cell is endowed with enzymes for the dehydrogenation of these four metabolites. No detailed analysis was made of the main part of the dye-stimulated respiration which is based on utilization of tissue metabolites. The respiratory quotient (0.85) of these processes suggested oxidation of protein and fat. (*c*) The oxygen-activating component of respiration was estimated by measuring the spontaneous oxygen consumption of cartilage. The activity of this component declined 65 per cent from infancy to old age. This decline coincided and progressed with appearance and extension of the degenerative changes in cartilage.

Gradual failure of spontaneous respiration with aging hinders the use of the dehydrogenatic processes which are important in cellular anabolism. When to this is added the diminution of cell content, it must follow that the intrinsic integrity of aged articular cartilage is materially weakened.

DISCUSSION

DR. KARL MEYER, New York: Cartilage seems to be especially suited for a study like this because apparently its metabolism is fairly constant over the period of time in which one is working, and, second, because it is a relatively simple tissue in which one can study not only the energy production but also for what chemical processes the energy is used. To connect the energy metabolism with the production of chondroitin, sulfuric acid seems to be possible since there are methods available to determine the amount of hexosamine and from that figure calculate the amount of chondroitin sulfuric acid in cartilage. It would further be interesting to study the production of glycuronic acid in cartilage. Is the failure of oxidative processes which the authors demonstrated connected with a failure to oxidize dextrose or a dextrose equivalent into glycuronic acid? How does this total metabolism of cartilage change with age? It is said that apparently the total volume of the cartilage is not changed with age, though some of its components are. This may mean that the aging cells must produce some components other than the young ones. Apparently chondroitin sulfuric acid is replaced by connective tissue or other fibrous tissue for the pro-

duction of which not so much energy may be required. The production of this fibrous tissue may require quite a different type of metabolic activity from that of young cartilage.

DR. MARIAN W. ROPES: The onset of degenerative joint disease in the cartilage makes study of the alterations of metabolism with age of special significance. The value of this work has been greatly increased by correlating the analytic results with the number of cells. The low rates of metabolism are in accord with the avascular nature of articular cartilage and its limited reparative ability. However, while such work is essential, it is also extremely difficult to control and interpret. Great caution is necessary in drawing conclusions to avoid misleading results which would tend to bring essential studies of this type into disrepute. The conflicting results in this study and that of Bywaters make further work necessary. Apparently some of the determinations of Bywaters were on young cartilage, so that the differences cannot be explained entirely on age. The values of oxygen consumption are in such a low range that errors are magnified and all factors in the method become significant. I should like to ask how thick the slices were, whether one could be sure that oxygen was reaching all cells; whether control slices, heated to kill the cells, were used; whether the sterility was carefully checked, and how long the experimental runs lasted. Also I should like to know whether the slices were perpendicular to the surface as would be essential for comparable distribution of cells, and whether consecutive slices were used for metabolic experiments and microscopic study, both for number of cells and for degenerative changes, for especially in cartilage with degenerative changes there are great variations from one area to another. In any case it would seem almost impossible to rule out the errors from the clustering of cells that is known to occur. Was the change in specific gravity of the matrix considered in estimating the cell mass? If cartilage cells are larger in old age, as has been suggested though not proved, the calculation of cell mass would be incorrect and much if not all of the change in oxygen consumption with age could be explained. The magnitude of glycolysis in proportion to oxygen consumption and the predominance of dehydrogenase activity over the oxygen activating system have been well shown by Dr. Bowie's work. Whether the low respiratory activity decreases with age seems less conclusively proved. Its significance in terms of energy is changed only from 170 to 135 per cent from youth to age. Finally, whatever metabolic differences exist between young and old cartilage, there is no evidence that they are the cause rather than the effect of degenerative changes.

DR. DAVID H. KLING, Los Angeles: Dr. Bywaters has proved that articular cartilage is a tissue of low metabolism. The objection of the authors that he worked with old cartilage of reduced metabolism does not appear to invalidate his results because he conducted a comparative study of metabolism of cynovial membrane and cartilage from the same joint. He found that the oxygen consumption per cell of cartilage was less than one one-hundredth of that of synovial cells and, although glycolysis was higher, it amounted to only one-eighth that of synovial membrane from the same joint. Articular cartilage is an avascular tissue. Nutrition is of less importance for maintenance of integrity of avascular tissues than protection. It was experimentally proved that, if articular cartilage is exposed to drying or to p_H values below 7, erosion and degeneration take place. Jones has demonstrated that friction due to movement of joints without lubrication results in heating and rapid deterioration of articular cartilage. This evidence indicates that the most important factor for the maintenance of proper lubrication and protection of the articular cartilage is the synovial fluid. Pathologic changes of this fluid, perhaps also disturbances of the blood supply of the synovial tissue with increased age, appear to be more significant than deficiencies of nutrition for development of degenerative changes of articular cartilage.

DR. OTTO ROSENTHAL, Philadelphia: The presence of glycolytic and dehydrogenatic enzymes in articular cartilage was shown by Bywaters when he found that cartilage split dextrose to lactic acid and consumed oxygen after the addition of methylene blue. The nature of the dehydrogenatic processes was not demonstrated by Bywaters. Dehydrogenases without oxygen-activating enzymes are of little value for the function of a cell. A cartilage cell endowed solely with glycolytic power could hardly produce the variety of substances which constitute its matrix. Therefore it seemed to us of interest when we found that young cartilage has a definite respiratory power and when it was possible to elucidate to some extent the nature of the dehydrogenatic processes. Qualitatively the metabolism of cartilage does not differ as greatly from that of other tissues as was assumed. A detailed study of the oxidative enzymes was not attempted because it would have required the use of tissue extracts. We restricted our studies to the reactions of surviving tissue. The presence of catalase, therefore, was not investigated. Indophenol oxidase is apparently present in cartilage, since paraphenylene-diamine is oxidized by the slices. As Dr. Meyer pointed out, it would be of importance to find out what the cartilage cell does with the energy it obtains from either glycolysis or respiration. To solve this problem we must study anabolism and catabolism of cartilage constituents such as chondroitin sulfuric acid. It might be worth mentioning that cartilage splits one constituent of this acid, namely galactose, and that the enzyme involved is different from the glycolytic enzyme. The mechanism of this enzymatic process remains to be solved. Since the respiration of cartilage is constant over a period of from three to five hours, it is not difficult to obtain reliable readings. The thickness of the slices was around 0.5 mm. in all the ages studied, i. e. the slices were sufficiently thin to guarantee optimal oxygen supply. Oxygen consumption as well as glycolysis and dehydrogenation disappear completely after immersing the vessel with the slices for six minutes in boiling water. I think we can deny with certainty the question as to whether a miscalculation of the cell content could have accounted for the respiratory decline in the aging cells. Our assumption that the cellular mass is proportional to the cell content of the fixed tissue is tentative. An estimate of the shrinkage of the tissue in the course of the embedding procedure and a separate determination of the specific gravity of the cells and of the matrix in the age groups were not possible. But we believe that the magnitude of the cellular activity was obtained without applying these corrections. Even if we disregard completely these data, the respiratory failure with aging remains a fact because the ratio of respiration to glycolysis decreases with advancing age to the same extent as the ratio of respiration to cell content. With regard to the cause of arthritis, we never claimed that the respiratory failure in aging cartilage is the only cause of degenerative arthritis, but we believe that it is an intrinsic factor of aging. So far I think it has been of some advantage to replace one vague term by a definite process.

Latent Brucellosis: Its Importance in Association With Joint, Muscle and Nerve Pain

DRS. WARD DARLEY, and R. W. GORDON, Denver: If the intradermal tests with Brucella antigen is a reliable index to Brucella sensitization, the use of the test in a large series of patients should be of value in indicating the possible importance of Brucella sensitivity in certain chronic illnesses, particularly those in which neuroskeletomuscular complaints are prominent. Of 1,027 "ailing" and 360 "well" individuals tested, 15.48 and 8.88 per cent respectively gave positive reactions. Of 159 positive reactors only fifty-four were found in whom a positive skin test was the sole objective finding and in whom there appeared to be no complicating neurosis. In this group neuroskeletomuscular complaints stood second in incidence (62 per cent). Of 124 patients with hypertrophic arthritis, 13.7 per cent gave positive reactions. Eighteen per cent of eighty-nine patients with infectious arthritis gave positive reactions. Symptom comparison of the skin negative cases in this group with the fifty-four uncomplicated reactors, except for the constancy of joint complaints, revealed in general a lower incidence for all the symptoms tabulated.

Of 301 patients with personality determined disorders 26.5 per cent were positive reactors, and of 159 reactors eighty, or 45 per cent, had maladjustment problems. Fifty-eight Brucella sensitive patients were found in whom the only other observations were functional in nature. Symptom comparison of this group with the fifty-four uncomplicated reactors revealed little difference

except a much higher incidence of nervous and emotional complaints. One hundred nonreactor cases of personality maladjustment were also studied (as a control group) and it was found that the incidence of neuroskeletomuscular complaints was essentially the same as in both the fifty-four uncomplicated reactors and in the group of fifty-eight cases.

In general we conclude, then, that Brucella sensitization is commonly found in patients with subjective neuroskeletomuscular complaints whether they have associated personality problems or not. It would appear to us that each individual skin positive case should be carefully evaluated as to Brucella immunity or activity and as to the presence of personality determined disorders before mapping out therapeutic procedures.

DISCUSSION

DR. EPHRAIM GOLDFAIN, Oklahoma City: If Brucellosis causes psychoneurotic complications, then naturally the reverse is true. Psychoneurotic persons when seen by physicians should be investigated for latent brucellosis. Specific treatment of these psychoneurotic patients should be carried on concomitantly with other treatment measures, even if it is only an aggravating factor rather than a true cause of the individual patient's symptom complex. Briefly I wish to set forth observations noted as a result of routine testing by means of agglutination, opsonocytophagocytic, and cutaneous tests all cases seen in which arthritic or rheumatic symptoms were present. Where objective arthritic observations are present and other causes which explain the presence of the arthritis are lacking, except positive agglutination, opsonic index and cutaneous tests, there will quite often present itself to the examining physician the following outstanding subjective and objective observations: 1. Periarticular swellings, often resembling a typical case of atrophic arthritis. 2. Cold, clammy skin of hands. 3. Lack of response to removal of apparent foci of infection. 4. Often lack of response to other therapeutic measures. 5. Presence on x-ray examination of a lack of bony tissue involvement yet the presence of swellings typical of atrophic arthritis. 6. Absence of marked secondary anemia. 7. Absence of streptococcus antibodies. 8. Moderately active red cell sedimentation test. 9. Quite regularly a high titer of agglutination for the Brucella organism as well as a high opsonic index test and a strongly positive persistent Brucella cutaneous test. 10. Neurasthenia.

DR. WILLIAM J. KERR, San Francisco: In recent years I have seen some of the more chronic or protracted conditions that may occur in connection with brucellosis. In general one sees a number of complications or later involvements similar to those seen in typhoid. I have seen osteomyelitis of the spine and osteitis of the bone of the face and the floor of the antrum, and a number of others have been observed and described. Drs. Darley and Gordon have brought up a question which has been in my mind for a long time. How can one differentiate the group of symptoms that these patients complain of from those seen in the neurotic or psychoneurotic patient or in the psychotic patient? I think the authors have shown that most of the symptoms are exactly those seen in persons who have been ill for a long time with any chronic disease. It is this same group of symptoms which are difficult to differentiate from the symptoms of toxic goiter. Aside from the greater incidence of fever in this group there is some suggestion that they may have chronic or prolonged effects of brucellosis, and there was little else that seemed of great significance. However, those who were chosen for the group of psychoneuroses or insanity states show a preponderance of symptoms in favor of anxiety states. I have seen quite a number of patients who were known to have had brucellosis and who have been observed for a period of several years. It seemed to me that in them the most difficult symptoms to control were the symptoms which have been described. I believe that there is no proof as yet that they are due to the infection itself or to the lasting effects of some hidden focus of some other infection of this general type, but they appear to belong to the symptoms seen in any chronic invalid. If one undertakes to treat these symptoms by vaccines, the only effect will be by suggestion. This may be justifiable, but I think it is bad medical practice, particularly since it tends to mislead one as to values in treatment.

DR. D. MURRAY ANGEVINE, New York: We have taken a good many agglutination tests on serum as well as a good many cutaneous tests both for brucellosis and for abortus infection. In no patient from the Arthritis Clinic of the New York Hospital have we found any indication that brucellosis is a serious problem in relation to arthritis in New York City.

DR. W. PAUL HOLBROOK, Tucson, Ariz.: The authors have presented a series of control cases and have proved that the presence of a previous brucellosis as evidenced by a positive cutaneous test has no more to do with the etiology or joint manifestations than a positive tuberculin test. In my part of the Southwest the finding of rheumatoid arthritis with brucellosis is certainly uncommon. I have always doubted that brucellosis can produce a typical rheumatoid arthritis. It may be that it does occasionally.

DR. R. H. FREYBERG, Ann Arbor, Mich.: In Ann Arbor we studied twenty-five patients who had typical rheumatoid arthritis and twenty-five other patients who came to the hospital complaining of symptoms of a rheumatic nature but whose disease was not characteristic of any common type of arthritis. We studied these two groups of patients in the same way by doing blood cultures for Brucella, by doing cutaneous tests and opsonocytophagic indexes, taking careful histories and making physical examinations. None of the patients in the first group had any evidence that we could consider indicated or allowed a diagnosis of brucellosis. Three persons in the second group had what we considered to be definite evidence of brucellosis, and six others had "possible brucellosis." From this study we concluded that joint symptoms frequently exist with brucellosis: acute arthritis may occur, but chronic joint inflammation seldom if ever results from brucellosis.

DR. E. STERLING NICHOL, Miami, Fla.: I would offer a word of caution about assuming too definitely that the neuromuscular complaints in chronic brucellosis are due to psychoneurosis rather than to the infection. Individuals afflicted with chronic brucellosis do poorly in the climate of southern Florida. After seeing a number of so-called psychoneurotic patients experience gross exaggeration of their neuromuscular complaints after migration to the latitude of southern Florida, I am of the opinion that an occult Brucella infection may account for some of these complaints, a view which has been substantiated in some instances by clinical investigation.

DR. WARD DARLEY, Denver: The biggest questions that confront most of us (as far as Brucella sensitization is concerned) are decisions as to the cause of the patient's symptoms and the selection of cases for treatment. I feel that one still has to depend for the most part on clinical judgment, but it is only natural that one should turn to the laboratory for help. Given a positive cutaneous test, one should decide whether the patient is immune and thus from the practical standpoint whether he is still actively infected. I am afraid that unless the various tests are properly understood they will only add to the confusion already so evident in the study of brucellosis. The agglutination reaction is usually negative in the skin positive cases. There is no agreement among investigators as to how strong an agglutination one must have before infection is considered active. Some investigators consider titrations as low as 1:10 as significant. Most investigators require titrations of 1:80 or more before considering a given case as one of active infection. There were about twenty of our patients who had agglutinations of 1:50 or above. The opsonic phagocytic index theoretically should be of value. It is a complicated procedure and its interpretation is a matter of controversy, even if done correctly. The complement fixation reaction may offer a possible solution to this problem. To date, reports in the literature are few as far as its application to brucellosis is concerned. The sedimentation rate is of no help. I do not want to be misunderstood regarding the relationship between brucellosis and psychoneurosis. I do not think that latent brucellosis can be used as an explanation for psychoneurosis. It is possible that Brucella sensitization may render an individual more susceptible to personality maladjustment. We do not feel that it can be a primary cause. In our experience psychotherapy, in these instances, is more important than specific anti-Brucella therapy.

(To be continued)

Current Medical Literature

AMERICAN

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Titles marked with an asterisk (*) are abstracted below.

American Journal of Clinical Pathology, Baltimore

10:673-770 (Oct.) 1940

*Vitamin K in Hemorrhagic Diseases of Infants and Children. I. N. Kugelmass, New York.—p. 673.
Actinomycosis: Review with Detailed Clinical and Autopsy Reports of One Case Each of Intestinal and Ovarian Forms. L. S. Auster, New York.—p. 688.
*Primary Splenic Neoplasms. S. A. Goldberg, Newark, N. J.—p. 700.
Stromal Tumors of Choroid Plexus. A. F. Liber and J. R. Lisa, New York.—p. 710.
Unusual Manifestations and Pathology of Congenital Syphilis. K. E. Landé, Hagerstown, Md.—p. 736.
Influence of Cobalt on Iron Transportation and Storage: Chemical and Histologic Study. K. Kato and Vivian Iob, Chicago.—p. 751.

Vitamin K in Hemorrhagic Diseases of Children.—Kugelmass points out that the wide range of fluctuation (a deficiency of as much as 80 per cent with no hemorrhagic manifestations and an excess up to 300 per cent without thrombotic phenomena) indicates the instability of the clotting mechanism when disease affects its components. Several hundred blood clotting determinations have led to the conclusion that prothrombin is not a determining factor in purpura, hemophilia or scurvy of infancy and childhood except in rare hemorrhagic disturbances (hemorrhagic disorders of the newborn, neonatal icterus gravis, hepatic pseudohemophilia and hereditary pseudohemophilia). They may be related to intestinal disorders preventing biliary absorption of vitamin K or to hepatic or bone marrow dysfunction interfering with the synthesis and subsequent liberation of prothrombin into the blood. Therefore vitamin K may raise blood prothrombin if intestinal absorption and reticulo-endothelial synthesis are adequate. Each case of neonatal hemorrhagic disease differs in its cause and course but the bleeding is invariably due to prothrombin deficiency. Nine of ten such cases showed marked depression in the prothrombin content of the blood with a corresponding lowering in the clotting time. Since the determining factor was consistently a decreased blood prothrombin the condition was designated acute hypothrombinemia. The mild form of the disease is undoubtedly self limited, as two of the ten cases were discovered only during routine clotting time determinations. Severe cases respond poorly to all forms of therapy in spite of early diagnosis. These have been associated with prenatal transmission of the disease indicated by the lowered prothrombin content of the expectant mother's blood. Vitamin K appears of equal value with blood transfusion in mild cases, the one forming prothrombin and the other providing it. But mild cases offer no final criteria because coexisting hematogenic jaundice may diminish its absorption and utilization and thus interfere with its synthesis. That vitamin K raises the prothrombin levels is no index of its efficacy in the presence of hemorrhagic disease characterized by injury to the reticulo-endothelial system. Therapy should not be limited to a precursor of prothrombin when the active substance, blood, is available. The routine use of vitamin K to protect the newborn from possible hemorrhagic disease is not indicated as there is ample prothrombin for clotting shed blood. Further abnormally high prothrombin levels cannot prevent blood from oozing through a damaged vascular system unless the entire circulation is clotted. The contention that the prevention of neonatal hemorrhagic diseases will diminish intracranial hemorrhage is only partially true, as the former is a disease of the blood and the latter a result of trauma to the vascular system. A normal blood coagulability does not preclude vascular injury and vice versa. The two diseases are more often mutually exclusive than coexistent. In icterus gravis neonatorum the bleeding tendency depends more on the extent of damage to the liver parenchyma than on the degree of jaundice. The low blood prothrombin is probably a secondary manifestation of progressive hepatic dysfunction which interferes with the synthesis of prothrombin. A case of obstructive jaundice with hemorrhagic manifestations cleared on the second day following 1 cc. of vitamin K in oil given in conjunction with bile acids three times a day. The blood picture was within normal limits after a week of severe jaundice. In hepatic pseudohemophilia accompanying infectious invasions or chemical poisoning the bleeding is due to a decreased production of prothrombin or fibrinogen or both in the liver with a resultant diminution in their concentration in the blood characterized by a markedly prolonged clotting time. A case of infective jaundice with hemorrhagic manifestations responded favorably to vitamin K. Marked hemorrhagic episodes in this condition are primarily determined by the qualitative defect in platelets, and therefore vitamin K is not indicated unless there is a coincident decrease in prothrombin during mild interim attacks.

Primary Splenic Neoplasms.—Goldberg reports one hemangioma cavernosum removed surgically as spleen and three primary neoplasms of the spleen: a solitary hemangioma cavernosum, a solitary microcystic lymphangioma and a multiple macrocystic lymphangioma. The three primary cases were encountered among 575 necropsies, in which there also were ten secondary malignant neoplasms. These ten neoplasms were obtained from ninety-eight cases of carcinoma, giving a greater incidence (9.8 per cent) of splenic metastases than is recorded in the literature. The case of cavernous hemangioma of the spleen consisted of a solitary nodule in an otherwise normal spleen and was apparently an early neoplasm. The cases reported in the literature are mostly large cystic hemangiomas. The microcystic lymphangioma consisted of a solitary nodule 8 mm. in diameter, apparently an early growth in an otherwise normal spleen. The stroma was quite cellular in places, containing lymphocytes, endothelial cells and budding vessels, and therefore the lymphangioma belongs in the category of a neoplasm. The macrocystic lymphangioma was composed largely of lymph spaces separated from one another by a fibrous and cellular stroma, and a few blood vessels. These last two tumors appear to be real neoplasms rather than simple telangiectatic areas, since the lymph spaces are separated by a cellular stroma containing budding vessels. They conform to Ewing's description of cystic and cavernous lymphangioma. The bulky hemangioma cavernosum removed from the region of the spleen is considered spleen. The light area in the center of this tumor was composed mostly of mucoid connective tissue and possibly was a stage in the formation of fibroma said to develop from a cavernous hemangioma.

American Journal of Physiology, Baltimore

130:613-814 (Oct.) 1940. **Partial Index**

Pressor Response to Adrenalin in Course of Traumatic Shock. A. M. Freedman and H. Kabat, Minneapolis.—p. 620.
Measurement of Venous Pressure in Man Eliminating the Hydrostatic Factor. J. P. Holt, Chicago.—p. 635.
Reciprocal Innervation in Small Intestine. R. Hodes, Boston.—p. 642.
*Dark Adaptation and Experimental Human Vitamin A Deficiency. S. Hecht and J. Mandelbaum, New York.—p. 651.
Growth and Development of Six Generations of Thymectomized Albino Rats. A. Segaloff and W. O. Nelson, Detroit.—p. 671.
Changes in Respiration on Inflation and Deflation of Chest. J. K. W. Ferguson, Toronto.—p. 675.
Temperature Regulation in Chronic Cervical Cats. G. Clark, Chicago.—p. 712.
Hemolytic Action of Chyle. L. W. Freeman and V. Johnson, Chicago.—p. 723.
Effect of Climate on Volumes of Blood and of Tissue Fluid in Man. W. H. Forbes, D. B. Dill and F. G. Hall.—p. 739.
Action of Heparin, Serum Albumin (Crystalline) and Salmine on Blood Clotting Mechanisms (in Vitro). J. H. Ferguson, Ann Arbor, Mich.—p. 759.
Rate of Respiratory Adjustment to Postural Change. M. H. Soley and N. W. Shock, San Francisco.—p. 771.
Effect of Oxygen Tension of Inspired Air on Respiratory Response of Normal Subjects to Carbon Dioxide. N. W. Shock and M. H. Soley, San Francisco.—p. 777.

Dark Adaptation and Vitamin A Deficiency.—Hecht and Mandelbaum determined the dark adaptation of seventeen men from 21 to 30 years of age before, during and after their stay on a vitamin A deficient diet. The data show that cone and

rod visual functions are affected by the diet. The cone thresholds rise less than the rod thresholds, but their behavior is approximately parallel. The best single criterion of these changes is the final rod threshold after thirty minutes in the dark. When subjected to the deficient diet fourteen of the seventeen subjects responded by an immediate and unmistakable rise in visual threshold which continued for the duration of the diet. The other three men required twenty-two, fifty-five and sixty days respectively before giving a clear and continuous rise in threshold. None of the subjects showed any cutaneous symptoms and only two were actually aware subjectively of their raised visual thresholds. Partial recovery was accomplished by some individuals after single large doses of vitamin A. The recoveries were never complete and always temporary. Permanent recovery from the vitamin A deficient diet was slow. The fastest return to normal was six weeks; the slowest subject to return to normal maintained a high threshold for more than three months but recovered completely after a year. Efforts to influence the visual responses by supplementation with other vitamins during and after the diet deficient in vitamin A yielded negative results.

Archives of Otolaryngology, Chicago

32:611-830 (Oct.) 1940

Appraisal of Four Years' Experience with Round Window Grafts for Deafness. W. Hughson, Abington, Pa.—p. 611.
Acute Infections of Epiglottis. J. M. Brown, Los Angeles.—p. 631.
Osteoma of Mastoid: Report of Two Cases. W. L. Simpson, Memphis, Tenn.—p. 642.
*Plummer-Vinson Syndrome: Report of Two Cases. J. D. Kernan, New York.—p. 662.
The Saccule: Observations on a Differentiated Reenforced Area of Saccular Wall in Man. H. B. Perlman, Chicago.—p. 678.
Cancer of Nasopharynx. H. E. Martin, New York, and J. V. Blady, Philadelphia.—p. 692.
Conservative Treatment of Sinusitis in Children. R. Gewanter, Long Island City, N. Y.—p. 728.
Intracranial Pathways of Infection from Diseases of Sphenoid and Ethmoid Sinuses. R. Kramer and M. L. Som, New York.—p. 744.
Development of Otic Capsule: V. Residual Cartilages and Defective Ossification and Their Relation to Otosclerotic Foci. T. H. Bast, Madison, Wis.—p. 771.
Anatomy and Physiology of Ear. J. R. Richardson and E. M. Holmes, Boston.—p. 793.

Plummer-Vinson Syndrome.—Kernan discusses the anemia, dysphagia, glossitis and achlorhydria of the Plummer-Vinson syndrome, its pathologic picture and the possibilities of carcinoma. The blood picture is that of essential hypochromic anemia. Occasionally atrophy of the mucous membrane at the mouth of the gullet leads to dysphagia. This confirms the diagnosis, especially if spoon nails and paresthesias are present. The syndrome is nearly always found in women and is frequently accompanied by achlorhydria and occasionally by splenic tumor. The dysphagia may be caused by (1) spasm due to hysteria or to atrophic or painful lesions which lead to understimulation or overstimulation of the sensory arc of the swallowing reflex or (2) by bands or webs across the mouth of the esophagus. The glossitis takes the form of atrophy of the lingual papillas. The tongue is smooth, red and painful. It is shrunken as in other severe anemias. Lack of hydrochloric acid interferes with absorption of iron from the food; hence the anemia. Recovery is quicker if hydrochloric acid is given with the iron treatment. Achlorhydric anemia and the syndrome are not necessarily related. Vinson's definition of the syndrome indicates that there is no pathologic picture as there is no organic lesion. Yet those who have found organic lesions of the esophagus describe a pathologic picture. In one of the author's two cases the mucous membrane showed thinning of the epithelial layer, with ulceration. Dense collagenous tissue or one infiltrated with lymphocytes replaced the lamina propria and submucosa. There was destruction of the muscularis mucosae. In the muscularis there was moderate fibrosis. A number of workers state that there is a close relation between the lesions at the upper end of the esophagus and carcinoma at this site. Both conditions are frequent in women and the sequence is too frequent to be a coincidence. The esophageal lesion is at times so slight as not to be suspected until the esophagoscope is withdrawn, when cracks and abrasions make it evident. The author does not report his two cases as instances of the Plummer-Vinson syndrome but as cases showing a connection between gastric disease and atrophic conditions of the esophagus. The first case was obviously a case of dietary deficiency, as evidently duodenal leakage drained away much of the necessary nourishment. The ulceration and healing of the esophagus appeared as that of the Plummer-Vinson syndrome. The author does not think that esophagoscopy had anything to do with the patient's death. The second case he believes explains the formation of bands and adhesions. There must have been extensive ulceration. The ulcerated folds falling together might adhere. When the folds were subsequently pulled apart, webs and bands formed, some even bridging the lumen. He has no doubt that esophagoscopy caused the mediastinitis and death of this patient. The tissues of such an esophagus, long diseased and very fibrotic, were easily torn. Even without an actual rupture, leakage might be sufficient to cause infection of the mediastinum.

Florida Medical Association Journal, Jacksonville

27:165-212 (Oct.) 1940

Some Observations on Coronary Occlusion. R. H. Knowlton, St. Petersburg.—p. 177.
Correlating History, Clinical and Electrocardiographic Findings in Diagnosis of Coronary Occlusion. T. Z. Cason, Jacksonville.—p. 180.
The Aftermath of Coronary Occlusion. E. S. Nichol, Miami.—p. 182.
Surgical Treatment of Essential Hypertension. G. D. Lilly, Miami.—p. 188.
Anesthesia. J. B. Quicksall, St. Petersburg.—p. 191.

Journal of Bone and Joint Surgery, Boston

22:895-1152 (Oct.) 1940. **Partial Index**

Treatment of Clawfoot. W. H. Cole, St. Paul.—p. 895.
Treatment of Osteogenic Sarcoma. A. B. Ferguson, New York.—p. 916.
Surgical Treatment of Osteo-Arthritis of Hip Joint. M. S. Henderson and G. A. Pollock, Rochester, Minn.—p. 923.
Clinical Study of 100 Patients Subjected to Simple Exostosectomy for Relief of Bunion Pain. R. T. McElvenny, Chicago, and F. R. Thompson, New York.—p. 942.
*Local Use of Sulfanilamide in Various Tissues. J. A. Key, C. J. Frankel and T. H. Burford, St. Louis.—p. 952.
*Sulfanilamide and Internal Fixation in Treatment of Compound Fractures. W. C. Campbell and H. Smith, Memphis, Tenn.—p. 959.
Injury to Intervertebral Disks During Spinal Puncture. M. Gellman, Baltimore.—p. 980.
Intrusion of Smith-Petersen Nail into Acetabulum. H. W. Harris, Ann Arbor, Mich.—p. 999.
*Treatment of Cerebral Palsies. W. M. Phelps, Baltimore.—p. 1004.
Legg-Perthes Disease of Hip: Its Early Roentgenographic Manifestations and Its Cyclic Course. A. B. Gill, Philadelphia.—p. 1013.
Growth Following Fusion for Tuberculosis of Knee in Children. S. L. Haas, San Francisco.—p. 1048.
Malunion of Fracture of Head of Metacarpal Bone (Knuckle Fracture): Simple Operation for Correction. E. J. Haboush, New York.—p. 1054.
Simple Method of Reduction and Fixation of Compression Fractures of Spine. E. Parnall, Minot, N. D.—p. 1072.
Tuberculosis of Greater Trochanter and Trochanteric Bursas. J. D. Wassersug, Middleboro, Mass.—p. 1075.
Aseptic Necrosis of Bone Occurring in Caisson Disease: Case Report. W. A. Walker, New York.—p. 1080.
Method for Maintaining Cut Edges of Split and Bivalved Casts in Accurate Apposition. R. C. Rounds, Denver.—p. 1088.
Accessories for Wedging Plaster Jacket in Treatment of Scoliosis. C. W. Goff and J. H. Aldes, Hartford, Conn.—p. 1090.

Local Use of Sulfanilamide.—During the last year Key and his associates used sulfanilamide as a routine in contaminated wounds and in clean operative wounds with considerable damage to the tissues, when infection was especially feared or particularly undesirable and when foreign materials (bone grafts and wire or screws) were left in the wound. They suggest that the drug be sterilized before it is placed in the wound. Through studies on animals the authors find that powdered sulfanilamide slightly inhibits the primary healing of the wound but not to such a degree as to contraindicate its use in clean operative wounds. Its repeated use in open infected wounds does not seriously interfere with their healing. The authors feel free to implant sulfanilamide at will in clean operative wounds provided the powder is sterile. The powder should be crushed if it is lumpy after autoclave sterilization and spread thinly over the surface of the wound after hemostasis has been effected and just before the wound is sutured. Powdered sulfanilamide in a wound is similar to a test tube experiment in which a concentration of the drug of approximately 1,000 mg. is brought into contact with any bacteria which may be present. In such concentrations the drug is effective against small numbers of staphylococci and of Welch's bacilli, and against large numbers of streptococci. When it is considered that local infected lesions contain large numbers of bacteria growing in

a favorable medium which contains peptone-like substances and that only a relatively low concentration of the drug is obtained by systemic administration of sulfanilamide, it is obvious why such administration is not effective.

Sulfanilamide and Internal Fixation for Compound Fractures. — Campbell and Smith studied the prophylactic action of sulfanilamide on infection in fifty-four compound fractures including those with internal fixation. The results were sufficiently favorable to warrant further use of the drug. The cases of fractures are divided into three groups: fresh compound fractures, old compound fractures with a previous infection, and compound fractures with an active draining infection. In a portion of the first series, from 15 to 20 Gm. of sulfanilamide crystals was placed directly into the compound wound and the wound was closed without drainage. After twenty-four hours sulfanilamide was continued by mouth, from 15 to 20 grains (1 to 1.3 Gm.) every four hours. Of the ten cases of the thirty-five in the first group in which infection developed, cultures revealed Staphylococcus aureus in five, Welch's bacillus in three, Streptococcus haemolyticus in one and the organism was not recorded in one. These figures would suggest that sulfanilamide had a less favorable prophylactic action on staphylococcic and Welch's bacillus than on streptococcic infections. Sulfanilamide or azosulfamide was administered as a routine to the seven patients of the second group; the average dose was 8 Gm. of the former or 10 Gm. of the latter for from twenty-four to forty-eight hours prior to the operation and for from three to seven days after operation until there was no longer any danger of infection. No infections ensued in these seven cases. In the remaining twelve surgery was performed in the face of an active draining infection. The dosage of sulfanilamide, or azosulfamide, was similar to that administered in the presence of compound fractures with latent infections. Bacteriologic studies showed Staphylococcus aureus in three, Staphylococcus haemolyticus in two, Streptococcus haemolyticus in two, and the observations in five were not recorded. There have been no infections following internal fixation in ten; union has occurred in ten and it is too early for prognostication in two. In a number of the operative cases draining sinuses persisted for several weeks to months but the wounds ultimately closed and the bones united. In no case was it necessary to remove any of the plates, screws, nails or wires. The results in this group were the most striking of the entire series. Comparison with comparable controls shows better anatomic and functional results following internal fixation in conjunction with sulfanilamide than when internal fixation and sulfanilamide are not employed. The authors conclude that the present impression of sulfanilamide is favorable but that more extensive investigation must be carried out with sulfanilamide and other chemotherapeutic agents before accurate evaluation will be possible.

Treatment of Cerebral Palsies.—Phelps points out that, according to surveys in various parts of the country begun a few years ago, it may be assumed that there are at least 150,000 cases of cerebral palsy in the United States. A survey of children from 2 to 16 years of age in Maryland showed a yearly occurrence of seven cerebral palsy births per hundred thousand of population. In other parts of the country surveyed this ratio is fairly constant. The percentage of cases found in the Negro race is much lower than in the white race. A study to determine what percentage of patients had sufficiently high mental status to become worthwhile members of society showed that, if the physical difficulties could be alleviated, 68.8 per cent had good mental ability and that 72 per cent have a mild or moderate handicap. The problem of the cerebral palsies includes a large number of patients who would justify the time and expense of treatment. Severity of involvement is not always a contraindication to treatment. Treatment depends on a careful diagnosis of the particular kind of cerebral palsy: spastic, athetoid or ataxic. A complete muscle examination should be made in all cases. No operation should be performed on a spastic muscle without examination, as the condition of the antagonists is often the deciding factor in determining the procedure. In conservative treatment the flaccid and weak muscles must be protected from the weakening effect of undue stretching, and the spastic muscles from the strengthening effect of the stretch reflex. With selective massage, careful exercise, appropriate splinting and protection a great change in muscle balance may be attained. The amount of surgery apparently necessary at first will be greatly diminished. In athetosis a muscle examination will demonstrate those muscles which move involuntarily and those which do not. Athetosis seems better conceived as an involuntary attempt to move a joint in a certain way than as an involuntary stimulation of any individual muscle. Therefore surgical intervention on the muscles, nerves or tendons has little effect. Joint stabilizations are exceedingly difficult. The discomfort of the patient following the operation is marked and there is much difficulty with pressure sores. In general, operative procedures are unsuccessful. In severe cases Putnam's procedure is helpful; it quiets the athetosis but does not increase function. The further use of curare should be watched with interest. Carefully graded and prolonged relaxation beginning with the least athetoid parts of the body and extended to the more athetoid extremities combined with motion from the relaxed position eventually brings satisfactory results. The treatment of ataxia is that of training the voluntary motor centers to take over the function of the damaged balance mechanism. It can be compared to the learning of any other skill, such as playing the piano, which in time is carried out almost without thought. Thus, with sufficient practice the skill of balance and directional control can be learned until eventually it becomes habitual. The ideal place to train these patients is in a school or institution where their physical and educational needs are met until such time as bad habits can be broken and rehabilitation carried out. There is great danger of old habits returning at home, because they are so closely bound up with the home environment. After discharge from the institution, treatment should be continued individually at least three times a week to insure fixation of progress. It should be decreased gradually over a period of years as skills are taught which take the place of exercises. Obtainable results lie in three fields—use of the legs, use of the arms and speech. Speech disorders are likewise spastic, athetoid or ataxic, and the same principles of treatment apply. Satisfactory results, judged by the standards of other crippling conditions, are obtained when care and treatment are sufficiently intensive.

Journal of Nutrition, Philadelphia

20:305-412 (Oct.) 1940

Intravenous Administration of Crystalline Amino Acids to Infants. A. T. Shohl and K. D. Blackfan, Boston.—p. 305.
Fat as Factor in Healing of Rickets with Vitamin D. A. Knudson and R. J. Floody, Albany, N. Y.—p. 317.
Determination of Ascorbic Acid in Evaporated Milk, Powdered Milk and Powdered Milk Products. W. W. Woessner, C. A. Elvehjem and H. Schuette, Madison, Wis.—p. 327.
Modification of Line Test Applicable to Chicken Vitamin D Assay. E. W. McChesney and E. Homburger, Rensselaer, N. Y.—p. 339.
Composition of Gains Made by Rats on Diets Promoting Different Rates of Gain. Marjorie Pickens, W. E. Anderson and A. H. Smith, New Haven, Conn.—p. 351.
Influence of Fat on Calcium and Phosphorus Metabolism. J. H. Jones, Philadelphia.—p. 367.
Influence of Dietary Riboflavin on Content of This Vitamin in Chicken Tissue. A. Z. Hodson, Ithaca, N. Y.—p. 377.
Comparative Assimilation of Fluorine by Growing Rats During Continuous and Intermittent Dosage. Margaret Lawrenz, H. H. Mitchell and W. A. Ruth, Urbana, Ill.—p. 383.
Availability to White Rats of Phosphorus in Soybean and Red Clover Hays, Dorothy E. Williams, Florence L. MacLeod and Elsie Morrell, Knoxville, Tenn.—p. 391.
Prevention and Cure of Nutritional Muscular Dystrophy in Rabbit by Alpha-Tocopherol in Absence of Water-Soluble Factor. C. G. Mackenzie, M. D. Levine and E. V. McCollum, Baltimore.—p. 399.

Journal of Pharmacology & Exper. Therap., Baltimore

70:165-244 (Oct.) 1940. **Partial Index**

Actions of Methyl-Atropine Nitrate (Eumydrin). J. D. P. Graham and S. Lazarus, Glasgow, Scotland.—p. 165.
Changes in Blood Pigments Associated with Prolonged Administration of Large Doses of Acetanilid and Related Compounds. P. K. Smith, New Haven, Conn.—p. 171.
Effects of Intravenous and Intraperitoneal Introduction of Polyvinyl Alcohol Solutions on Blood. W. C. Hueper, J. W. Landsberg and L. C. Eskridge, New York.—p. 201.
Toxicity, Treponemicidal Activity and Potential Therapeutic Utility of Substituted Phenylarsenoxides. H. Eagle, Baltimore; G. O. Doak; R. B. Hogan, Baltimore, and H. G. Steinman.—p. 211.
Comparison of Digoxin with K-Strophanthosid. J. M. Walker, Oxford, England.—p. 239.

Kentucky Medical Journal, Bowling Green

38:423-470 (Oct.) 1940

Aims and Aspirations. A. Bell, Hopkinsville.—p. 424.
Lung Abscess. A. E. Grimes, Lexington.—p. 430.
Evolution of Our Knowledge of Tuberculosis. O. O. Miller, Louisville.—p. 434.
Management of Patients with Acute Myocardial Infarction. T. R. Harrison, Nashville, Tenn.—p. 442.
Intestinal Obstruction. B. E. Caywood, Danville.—p. 446.
Pathology of Primary Tuberculosis. B. L. Brock, Louisville.—p. 450.
Clinical Symptoms of Tuberculosis in Children. W. W. Nicholson, Louisville.—p. 452.
Extrapulmonary Tuberculosis. L. Palmer, Louisville.—p. 454.
Treatment of Tuberculosis in Children. O. O. Miller, Louisville.—p. 456.
Discussion of Sprue Syndrome. M. H. Thompson, Louisville.—p. 457.
Surgical Treatment of Peptic Ulcer. J. M. Frehling, Louisville.—p. 460.
Anemia as a Problem for the Dermatologist. H. Gordon, Louisville.—p. 464.

Maine Medical Association Journal, Portland

31:267-290 (Oct.) 1940

Estimating the Operative Risk. E. E. O'Donnell, Portland.—p. 267.
Pitfalls of Surgery. E. H. Risley, Waterville.—p. 270.
Estimation of Operative Risks and Choice of Anesthesia. G. Clapperton, Lewiston.—p. 274.
Postoperative Management. W. V. Cox, Lewiston.—p. 277.

Michigan State Medical Society Journal, Lansing

39:729-808 (Oct.) 1940

Jaundice: Differential Diagnosis and Treatment. W. Walters, Rochester, Minn.—p. 747.
Anesthesia in Shock. F. J. Murphy, Detroit.—p. 755.
*Impediment to Circulation: Occasioned by Pulmonic Interstitial Emphysema and Pneumomediastinum. C. C. Macklin, London, Ont.—p. 756.
Carpal Bone Injuries: Conservative Treatment. H. W. Woughter, Flint.—p. 759.
Cancer of Uterus: Plea for Adequate Irradiation. H. S. Collisi, Grand Rapids.—p. 763.
Virus of Poliomyelitis: Survival for Over Six Months in Feces of a Contact. S. D. Kramer, Lansing.—p. 766.
*Hyperactive Carotid Sinus Reflex: Clinical Experiences. B. E. Goodrich, Detroit.—p. 768.
Chronic Sinus Disease: Biologic Factors. R. W. Teed, Ann Arbor.—p. 772.
Lower Leg Fractures: Some Practical Considerations in Treatment. C. E. Maguire, Detroit.—p. 779.
Hydrorrhea Gravidarum. T. Wilensky, Eaton Rapids.—p. 783.
Iodide Content of Iodized Salt: Effect of Storage. D. M. Cowie and J. J. Engelfried, Ann Arbor.—p. 784.
Iodized Table Salt Carton: Analysis of Iodide Content of the Pasteboard. D. M. Cowie and J. J. Engelfried, Ann Arbor.—p. 785.
Meckel's Diverticulum: Invagination. H. A. Hanelin, Marquette.—p. 786.

Impediment to Circulation.—Macklin points out that air may leak into the connective tissue sheaths of the pulmonary arteries and veins from the surrounding alveoli and produce bubbles which interfere with the pulmonary circulation. With continued influx the air may travel along these sheaths to the mediastinum and accumulate there as large blebs which indent the heart and great vessels. The circulatory embarrassment resulting from this aberrant air may be serious and attended by dyspnea and cyanosis, and in children it may cause death. Often it clears up in a fortnight or less. Pulmonic interstitial emphysema is important clinically because of the encroachment by air bubbles on the space of the vascular system. Experimentally the air is propelled along the sheaths by the force of an artificial blast of air, but chiefly it is moved on by respiration, coughing, straining and other acts. Pulmonic interstitial emphysema and pneumomediastinum have been caused by excessive pressure in administrating intratracheal anesthesia, which complication may be fatal. Atelectasis is an important primary cause and must always be looked on as a threat of air invasion of the pulmonic vascular sheaths. A tendency to alveolar leakage would seem greater in some individuals than others and may be inherited. Too sudden inflation of a lung at operation may precipitate a leakage. Interstitial emphysemas and their associated pneumothoraces are never spontaneous. There always is an immediate exciting and predisposing cause. Roentgenograms, particularly oblique ones, are of diagnostic aid, and prompt appropriate therapy may save many lives, especially of children.

Hyperactive Carotid Sinus Reflex.—In a group of eighty-four individuals suffering from what appeared to be a hypersensitive carotid sinus reflex, Goodrich was able to duplicate the attacks by pressure on the carotid bulb. Sensitivity varied, so that only in the degree of reaction rather than in kind were some persons abnormal. Sixty-five of the eighty-four persons were men. The entrance complaint ranged from a few transient dizzy sensations to repeated attacks of syncope. Dyspnea, substernal pain, numbness and weakness occurred. Blindness, aphasia or aphonia were reported. Four patients had only gastrointestinal effects, although many had associated gastrointestinal symptoms. Earlier in this study the patients were exhaustively examined and many laboratory and technical tests were performed before a working diagnosis was made and treatment started. This consisted of advising patients to lessen spontaneous stimulation of the carotid sinuses by avoiding tight collars, abrupt motions, looking upward, singing and other activities leading to increased intracarotid pressure or to external mechanical stimulation. Medication to decrease the vagus reactions and to augment the activity of the sympathetic portion of the autonomic nervous system was utilized. Atropine or synthetic related drugs were most commonly used for vagus inhibition. Ephedrine sulfate and in some instances amphetamine sulfate was given and appeared to be helpful. Thyroid was used in the majority of cases. It was continued until all other medication was discontinued. If no symptoms recurred, continued thyroid medication depended on evidences of thyroid need, judged independently of the carotid sinus activity. Demonstrating to the patient that the origin of the attacks was known and that they could be produced at will restored his confidence. Correction of undesirable habits and ways of living resulted in the cessation of symptoms in one instance without any medication. Fifty-three of the eighty-four patients were treated, and thirty-two were completely relieved, thirteen were satisfactorily relieved (the major handicap was avoided), five required continuous treatment and two were not relieved; both of these had severe cerebral damage, and surgical denervation was not advised. Surgical denervation on the right carotid sinus of one patient brought about complete relief for one year, when symptoms recurred and the patient refused further treatment. The author concludes that hypersensitivity of the carotid sinus reflex becomes more frequent with advancing age and in persons with arterial hypertension. The symptoms are frequently considered heart attacks and digitalis, which is often prescribed, further sensitizes the reflex and exaggerates the symptoms. Electrocardiographic records indicate that the vagal effect is involved in the more dramatic symptoms.

New England Journal of Medicine, Boston

223:607-650 (Oct. 17) 1940

*Prevention of Diabetes. R. E. Haist, J. Campbell and C. H. Best, Toronto.—p. 607.
Thyroglossal Cysts and Sinuses: Study and Report of 198 Cases. R. E. Gross and M. L. Connerley, Boston.—p. 616.
Eczema in Infants and Young Children. L. W. Hill, Boston.—p. 624.
Pathologic Physiology of Bronchial Asthma in Children, with Reference to Role of Infection. H. N. Pratt, Boston.—p. 626.
Treatment of Bronchial Asthma in Children. E. A. Brown, Boston.—p. 629.
Acute Hepatitis, Jaundice and Abnormal Bleeding as Complications of Acute Appendicitis with Perforation. F. A. Simeone and J. D. Stewart, Boston.—p. 632.
Orthopedic Surgery. J. S. Barr, Boston.—p. 634.

Prevention of Diabetes.—Haist and his associates believe that sufficient information is now available to show that the production of diabetes in experimental animals by pituitary diabetogenic substances may be prevented by dietary means or by large doses of insulin. Their studies of the factors which affect the insulin content of the pancreas support those of previous workers who approached the problem from other directions. The experimental prevention of the diabetic condition by certain procedures makes it imperative that their curative effect be investigated. In considering the relation of their results to the treatment of diabetes in human subjects, the authors assume that the factors which prevent the condition from developing will also tend to limit its progress. Fasting, fat-feeding and insulin prevent or hinder the diabetic state under experimental conditions. These procedures affect the pancreas in a manner opposite to that of high carbohydrate diets and prevent the deleterious effects of anterior pituitary diabetogenic principles. There is no evidence that factors which rest the pancreas cause permanent damage to islet cells, whereas factors leading to overactivity may produce permanent changes. If a clinician is

convinced that the patient will be benefited by stimulation of the islet cells, diets rich in carbohydrate are indicated. When such diets are used in animals the islet cells may be protected by providing large amounts of insulin. However, if the physician believes that the pancreas should be rested, fasting, fat-feeding and insulin may be employed. When extensive destruction of the islet cells exists he may decide that there is no point in resorting to these procedures. Under other conditions a reduction of the strain on the remaining islet cells may restore some exhausted cells and thus improve the diabetic condition. This would seem to be particularly true in the early stages of the disease. In animals the exhausted cells retain for some time their ability to recover. The interval during which the cells of man may be exhausted but still be capable of recovery is unknown. Resting procedures prevent the degenerative changes from occurring in cells not already affected and permit restoration of the exhausted cells retaining such ability. Wide departures from the normal diet are permissible for only short intervals. Over longer periods nutritional requirements must be satisfied, especially for growing children, for whom only minor alterations are justifiable, in which case insulin may be the method of choice. The prophylactic administration of insulin to potentially diabetic patients may become an accepted clinical procedure in the future. The authors suggest that the incidence of diabetes should be investigated among two large and comparable groups of children with a familial history of the disease. One group should be given a normal diet and the second a diet as low in carbohydrate and protein and as rich in fat as is physiologically feasible. The second group might be given limited amounts of insulin. The authors appreciate the inherent difficulties of such a clinical investigation but believe that the goal justifies the endeavor.

Public Health Reports, Washington, D. C.

55:1801-1844 (Oct. 4) 1940

Rheumatic Heart Disease in Philadelphia Hospitals: Study of 4,653 Cases of Rheumatic Heart Disease, Rheumatic Fever, Sydenham's Chorea and Subacute Bacterial Endocarditis, Involving 5,921 Admissions to Philadelphia Hospitals from Jan. 1, 1930, to Dec. 31, 1934: IV. Influence of Season and Certain Meteorologic Conditions. O. F. Hedley.—p. 1809.

55:1845-1878 (Oct. 11) 1940

Rheumatic Heart Disease in Philadelphia Hospitals: Study of 4,653 Cases of Rheumatic Heart Disease, Rheumatic Fever, Sydenham's Chorea and Subacute Bacterial Endocarditis, Involving 5,921 Admissions to Philadelphia Hospitals from Jan. 1, 1930, to Dec. 31, 1934: V. Distribution by Locality of Rheumatic Conditions in Philadelphia. O. F. Hedley.—p. 1845.

Rickettsia Diaporica: Its Persistence in Tissues of Ornithodoros Turicata. G. E. Davis.—p. 1862.

Radiology, Syracuse, N. Y.

35:391-520 (Oct.) 1940

Pulmonary Overexpansion in Infancy and Early Childhood. R. A. Carter, Los Angeles.—p. 391.

Quality of Roentgen Rays: Effect on Tissue Dose and Clinical Importance. R. R. Newell, San Francisco.—p. 402.

Calibration of X-Ray Developer. G. M. Busanovich, Philadelphia.—p. 407.

Juvenile Osteochondrosis. C. A. Stammel, Fort Benning, Ga.—p. 413.

Radiation Therapy of Diphtheria Carriers. I. I. Kaplan, New York.—p. 425.

*Preoperative Irradiation in Carcinoma of Breast: Histologic Study. E. P. Halley, Stockton, Calif., and P. J. Melnick, Chicago.—p. 430.

Roentgen Findings in Caisson Disease of Bone: Case Reports. R. A. Rendich and L. A. Harrington, Brooklyn.—p. 439.

Roentgen Ray Examination in Individuals Suffering from Low Back and Sciatic Pain, with Examples of Some Lesions in Which Errors in Diagnosis May Readily Be Made. J. C. Bell, Louisville, Ky.—p. 449.

Myelography with Use of Thorium Dioxide Solution (Thorotrast) as Contrast Medium. B. H. Nichols and W. A. Nosik, Cleveland.—p. 459.

Effect of Iodized Oil on Meninges of Spinal Cord and Brain. L. H. Garland, San Francisco.—p. 467.

X-Ray Therapy of Hyperparathyroidism. E. A. Merritt and R. M. Caulk, Washington, D. C.—p. 477.

Sarcoid. E. R. Bader, Cincinnati.—p. 482.

Metastasis to Bone from Carcinoma of Gastrointestinal Tract. J. J. Stein, Hines, Ill.—p. 486.

Graphic Constructions for Localization, Mensuration and Reduction: Standard Symbols and Nomenclature. J. Kaufman, Brooklyn.—p. 489.

Preoperative Irradiation in Carcinoma of Breast.—Halley and Melnick observed radiation necrosis of tumor cells, associated with hyperemia, cellular infiltration, granulation tissue proliferation and fibrous and vascular changes after administration of massive doses in transplantable rat tumors. After fractional and protracted irradiation the most radiosensitive cells are destroyed by necrosis, but the remaining resistant cells undergo mutation-like alterations. The small daily doses transform them into pleomorphic abnormal forms, giant tumor cells which result from the direct action of radiation on the tumor cells and not from secondary reactive mechanisms. These giant cells do not degenerate by necrosis but by calcium deposition in their nuclei. There is no fibrosis and no vascular damage. Normal tissues recover from the small doses. Much of the fibrosis and vascular obliteration obviously results from damage to normal structures by irradiation at an intensity too high or because of too large individual or total doses to allow normal tissues to recover. In the usual case of carcinoma of the breast amputated from two to three months after irradiation, much intact and uninjured cancer is seen. This has been interpreted by pathologists as tumor tissue which has escaped the action of radiation. The authors think that perhaps the actual irradiation changes which occur earlier were missed. Accordingly, earlier amputation was requested, and data were collected on 21 cases of breast cancer in which tumor doses ranging from 1,200 to 4,500 roentgens were administered over periods of from eleven to forty-nine days. The interval between irradiation and operation ranged from one to forty-five days. Operation was done when desquamation was complete and the skin became smooth and dry, making surgical cleanliness feasible. The microscopic changes in these cases correlate with those found in animal tumors. It seems logical, therefore, to conclude that irradiation by fractional method acts directly on human breast tumor cells by producing early radionecrosis of sensitive cells and later by accumulation of mutation-like effects through succeeding generations of daughter cells. The latter mechanism may easily be the more significant. Damage to the tumor bed does not occur under usual fractional irradiation. Regrowth of surviving tumor cells appears in from four to six weeks after therapy ends. If this is true, it would seem that a short preoperative course of irradiation fails to achieve optimal tumor damage, as the mutation-like effects require from four to five weeks of irradiation. Since tumor bed damage is slight under the fractional method, this mutational mechanism can well be followed to a full second degree cutaneous reaction. Surgery done within two or three weeks after irradiation has the advantage of a tissue in which viable tumor cells have been decreased to a numerical minimum. Further delay faces regrowth of the tumor. After from eight to twelve weeks operation is done with the tumor almost in its preirradiation state, with the probability of invasion and metastasis. There have been no complications in the 21 cases in which operation followed an acute cutaneous erythema. Healing seemed more prompt in the irradiated patients.

Rocky Mountain Medical Journal, Denver

37:717-796 (Oct.) 1940

Mycotic Infection in Northeastern Colorado. A. E. Lubchenco, Sterling, Colo.—p. 741.

Modern Trends in Treatment of Acute Appendicitis. G. S. Postma, Denver.—p. 747.

Management of Labor in the Primipara. C. F. Moon, Omaha.—p. 751.

South Carolina Medical Assn. Journal, Greenville

36:267-300 (Oct.) 1940

Chronic Tetany: Is This Condition Common in Adults? E. B. Poole, Greenville.—p. 267.

Diagnosis and Management of Carcinoma of Colon. R. G. Doughty, Columbia.—p. 272.

Conservative Management of Pelvic Infections. J. A. Sasser, Conway.—p. 276.

Fracture of Skull with Unusual Complications. G. T. Tyler Jr., Greenville.—p. 281.

Tennessee State Medical Assn. Journal, Nashville

33:375-418 (Oct.) 1940

The Acute Abdomen. E. G. Kelly, Memphis.—p. 375.

Medical Participation in Selective Service. C. B. Spruit, Washington, D. C.—p. 382.

Gastrointestinal Symptoms of Urologic Conditions. C. H. Barnwell, Chattanooga.—p. 386.

Some Observations on the State Program for the Relief of Crippled Children. R. W. Billington, Nashville.—p. 393.

Etiology and Treatment of Eczema in Children. W. R. Graves, Memphis.—p. 400.

Private Practice of Public Health. J. C. Overall, Nashville.—p. 405.

FOREIGN

An asterisk (*) before a title indicates that the article is abstracted below. Single case reports and trials of new drugs are usually omitted.

British Journal of Children's Diseases, London

37:153-216 (July-Sept.) 1940

*Observations on Megacolon (Hirschsprung's Disease), with Special Reference to Association with Changes in Fundus Oculi and Hydrocephalus. C. Worster-Drought and J. Shafar.—p. 153.
Tracheotomy Twice for Laryngeal Diphtheria. A. R. Thompson.—p. 166.
Familial Vulnerability of Special Sites Toward Lesions of Congenital Syphilis: Ischemic Disturbance in Fingers of Two Sisters, Probably Due to Third Generation Syphilis. T. Anwyl-Davies, D. Nabarro and F. P. Weber.—p. 173.
Studies on Agglutinins and Agglutinogens in Blood of the Newborn. J. Halbrecht.—p. 175.

Megacolon Associated with Hydrocephalus and Optic Atrophy.—Worster-Drought and Shafar report a case of Hirschsprung's disease associated with hydrocephalus and optic atrophy. The somewhat obese blind boy aged 8 years was born prematurely of apparently normal parents and seemed to be of normal intelligence. He had suffered from obstipation since birth and for the last two years showed abdominal distention, with vomiting and diarrhea during the last year. Fecal discharges occurred every four days and were hard and bulky. A barium sulfate enema disclosed an enormous generalized dilatation of the colon. The encephalogram revealed symmetrical hydrocephalus. The optic fundi presented the picture of advanced bilateral optic atrophy with the vision of the right eye reduced to the mere perception of finger movements and with visual acuity of the left eye at 6/60. The authors, discussing the etiology and pathogenesis of the combined lesions, point out that in Hirschsprung's disease the hypertrophy cannot be accounted for by organic obstruction. The present tendency is to regard megacolon as a neuromuscular dysfunction due to an imbalance between the sympathetic and parasympathetic divisions of the autonomic nervous system. What constitutes the exact nature of the imbalance is still disputed. In hydrocephalus three mechanisms may be involved: (1) obstruction to the circulation of the cerebrospinal fluid, (2) defective absorption and (3) excessive secretion. Obstruction in the pathways of the cerebrospinal fluid is the commonest cause of congenital hydrocephalus and arises either from developmental abnormalities or from inflammatory processes or fibrosis, secondary to intracranial hemorrhage sustained intra partum. Defective absorption may arise from hypothetic infection involving the arachnoid villi or from maldevelopment of these structures. The cause of hypersecretion of cerebrospinal fluid by the choroid plexuses is still *sub judice*. Megacolon and hydrocephalus in the present case are assumed by the authors to have developed in utero. Hydrocephalus was, however, not progressive. Measurements of the circumference and diameter of the skull showed little variation from the normal. The underlying cause was either of a temporary nature or a defect that admitted of compensation. Congenital optic atrophy was regarded by the authors as secondary to hydrocephalus.

British Medical Journal, London

2:479-512 (Oct. 12) 1940

Review of Causes of Diabetes Mellitus. G. Graham.—p. 479.
Changes Occurring in Blood Stored in Different Preservatives. J. Dubash, O. Clegg and Janet Vaughan.—p. 482.
*Methods of Fluid Administration in Treatment of Surgical Shock: Experimental Comparison. R. A. King.—p. 485.
Use of Sulfur-Containing Compounds, Particularly Pentothal Sodium, in Conjunction with Sulfapyridine. E. J. R. Smith.—p. 488.
Use of Proflavine and Acriflavine in a Throat and Nose Department. G. Young and A. A. Charteris.—p. 489.

Fluid Administration for Surgical Shock.—King compared the value of several fluids for the treatment of experimental secondary shock in cats. Temporary recovery readily occurred in most cases of shock on the intravenous addition of physiologic solution of sodium chloride. The rise in blood pressure usually lasted from a few minutes to half an hour, after which it returned to the previous shock level or even lower. In severe shock intravenous physiologic solution of sodium chloride had little or no effect in raising the blood pressure. The rapid passage of the fluid through vascular endothelium into the tissues explains the temporary effect. Therefore the practicality of its use is limited. When too much is given, pulmonary edema occurs. Often about 20 per cent of the normal blood volume can be given in the early stages of shock. Cardiovascular disease and degenerative changes in the vascular endothelium from prolonged anemia and anoxemia greatly increase the risk of pulmonary edema. In order to avoid cardiac failure, intravenous fluids as a rule should be given slowly by the drip method. The risk of pulmonary edema is greatest in the advanced stages of shock. The intravenous administration of hypertonic solutions of sodium chloride in shock causes an immediate rise of blood pressure and the rise is prolonged. The response is sudden and so marked that it bears little relation to the amount of fluid given. The prolonged effect is partly due to the altered osmotic pressure of the plasma in the circulation which causes reabsorption of tissue fluids. Blood pressure in shock can frequently be restored by water absorbed from the intestine. However, in many cases the alimentary canal does not tolerate fluids and vomiting occurs, in which case fluids may be given subcutaneously. Isotonic sodium chloride or dextrose solutions given by subcutaneous injection over a prolonged period restore blood volume and pressure in shock. The effect is prolonged and contrasts remarkably with the temporary benefit obtained from physiologic solution of sodium chloride given intravenously. In certain experiments subcutaneous fluid produced no effect on the blood pressure, and the animals died without showing any signs of recovery. These fatal cases were always severe cases of long standing in which the circulation was probably too stagnant for subcutaneous absorption to occur. Hypotonic solution of sodium chloride by the subcutaneous route was rapidly absorbed in most cases of shock and caused a gradual sustained increase of blood pressure when the circulation was stimulated by hypertonic sodium chloride solutions and when an osmotic gradient was maintained. It is seen from the experiments that the state of shock may be benefited by the addition of fluid to the circulation. The clinical application of the foregoing principles of fluid administration is proceeding. Several cases of severe shock have been treated successfully. In 1 instance the blood pressure recovered from the low level of 30 mm. of mercury.

Lancet, London

2:411-442 (Oct. 5) 1940

*Treatment of Chronic Mastitis. H. J. B. Atkins.—p. 411.
Nomenclature of Influenza. F. L. Horsfall Jr., E. H. Lennette, E. R. Rickard, C. H. Andrewes, W. Smith and C. H. Stuart-Harris.—p. 413.
*Survival of Stored Red Cells After Transfusion. S. R. M. Bushby, A. Kekwick, H. L. Marriott and L. E. H. Whitby.—p. 414.
Survival of Stored Blood After Transfusion. M. Maizels and J. H. Paterson.—p. 417.
Survival of Transfused Erythrocytes of Stored Blood. P. L. Mollison and I. M. Young.—p. 420.
Asthmatic Attack Studied Through the Bronchoscope. A. L. d'Abreu.—p. 421.

Treatment of Chronic Mastitis.—Atkins states that a clinic for the investigation and treatment of chronic mastitis was attended by 212 patients with pain or with lumpiness in the breast. Previously he had defined chronic mastitis as "pain or lumpiness of the breast not due to bacterial inflammation, new growth or fat necrosis," a definition which frankly admits ignorance of the nature of the disorder. Early in the investigation it became clear that slight periodic pain in the breast and lumpiness sufficient to distinguish the breast from the surrounding subcutaneous tissue were commonly encountered among patients who never complained of their breasts. It was concluded therefore that the presence of these two symptoms did not necessarily imply abnormality. The definition of chronic mastitis thus tended to be confused until it was realized from microscopic studies that there was no definite distinction between the normal breast and the breast affected with chronic mastitis, the one merging imperceptibly into the other. A definition which makes such a distinction is undesirable and in fact impossible. In practice the author uses the term "chronic mastitis" to indicate pain or lumpiness in the breast of sufficient degree to bring the patient to the doctor. This implies that there are women experiencing these two symptoms who, because of fear of cancer or from some other psychologic cause, attend the mastitis clinic when their more phlegmatic

sisters with breasts similarly affected stay away. Thus a mastitis clinic becomes to some extent the resort of the apprehensive and the mentally unstable, and in assessing the effect of treatment it is important to take this psychologic element into account. The author did not feel justified in differentiating "mazoplasia" from "chronic cystiphorous epithelial hyperplasia," but the distinction between "epitheliosis" and "adenosis" has been of value in clarifying his idea of the histology of this disease, although he found that these two changes tend to occur together. Because of the psychologic element in painful nodular breast, it is necessary to exercise the most scrupulous control in investigating the effect of the various therapeutic agents. Six of the patients became pregnant while under observation and in 4 of them all symptoms disappeared between the fifth and sixth months. One of these 4 had had mastitis for many years and a previous pregnancy had caused the symptoms to disappear for eighteen months. The author examined the effect of estradiol benzoate given by injection or of the synthetic substance stilbestrol given by mouth. He found that the administration of estrogens in doses sufficiently large to affect the breast was found to be harmful, and it was thought that the microscopic changes were advanced by this substance. Androgens can alleviate the symptoms of most cases of chronic mastitis, but the beneficial effect is not permanent and undesirable concomitant effects, such as hirsuties, changes of voice, amenorrhea or disturbance of menstruation, may rob the treatment of its value. In 1 case of chronic mastitis, the only one of 212 to become malignant, carcinoma of the breast developed ten months after a course of testosterone propionate injections. The microscopic changes in the breast produced by androgens in doses up to the limit of tolerance are insignificant. Diathermy is of value in alleviating the pain in chronic mastitis, but its effect is liable to be only temporary.

Survival of Stored Red Cells After Transfusion.—According to Bushby and his associates, authorities have established organizations for supplying blood in large quantities in preparation for battle and air raid casualties. In the waiting period this stored blood was used for civil practice. Research was concentrated on the finding of diluents, anticoagulants, chemicals and other factors designed to ensure that the red cells would be sufficiently well preserved to survive in the recipient. Whether transfused red cells endure in the recipient cannot be determined by a simple blood count, because it does not show whether rises or falls in a total count are due to autogenous cells or to the transfused blood. The technic employed by the authors was to transfuse group O blood to a group A or group B patient. Counts of the recipient's blood were taken at intervals, a 1:101 dilution being made with the appropriate alpha or beta serum; the titer of the serums so used was 1:320. After being thoroughly mixed in the pipet, the contents were immediately expelled into a corked tube and incubated at 37 C. for an hour, being shaken at intervals of fifteen minutes. At the end of this time a drop was placed on a counting chamber and a count made of the "free" nonagglutinated cells which represent transfused group O cells. Before transfusion, the "nonagglutinable count," that is, the number of A or B cells not agglutinated by the particular alpha or beta serum, was determined for each patient. This number, which is assumed to be constant for each person, is subtracted as a correction from the "free" cell count before the number of surviving group O cells is calculated. The authors show in tables the percentage of cells surviving up to five consecutive days and at times up to twenty-five days, besides the quantitative fragility of the transfused sample and the amount of hemolysis present. When blood is collected into a 3 per cent solution of sodium citrate in the proportion of 100 cc. of citrate to 440 cc. of blood and stored at from 4 to 6 C., the following substances or procedures prolong the period of preservation of the red cells: adjustment of p_H to 5 (of no value in practice), dilution and addition of dextrose. Of the single factors, dextrose is the best. The enhancement given by dextrose and dilution, or dextrose plus dilution plus acidification, is recognizable as such, but the degree is not sufficient to justify utilization for practical storage of blood. For the acute hemorrhage and shock of the wounded the prime necessity is to restore blood volume adequately. With restoration of blood volume the efficiency of such oxygen-carrying elements is automatically increased. Brewer and his collaborators have reported that stored blood (containing dextrose) from ten to fourteen days old is as efficient as fresh blood for the treatment of acute hemorrhage. The survival figures determined by the authors confirm this statement and show that even older blood survives a reasonable time in the recipient and certainly long enough to keep a wounded man alive until he can receive complete surgical treatment. Such was the experience in recent campaigns, during which some 500 transfusions were given of blood from ten to thirty days old.

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25:423-770 (Nos. 5-6-7-8) 1940. **Partial Index**

Microscopic Prognosis of Nephropathy Due to Mercury. L. A. Surraco.—p. 423.
Obstetric Shock. R. Briquet.—p. 488.
*Obesity with Temporary Hypogenitalism in Prepuberal and Adolescent Age. J. M. Cerviño.—p. 521.
Interchange of Sex Hormones in Parabiosis. E. Fels.—p. 600.
Time as Pathogenic Factor in Experimental Gynecology. A. Lipschütz.—p. 651.
*Anovulatory Cycle in Women. E. Novak.—p. 687.
Allergy in Obstetrics. A. Peralta Ramos.—p. 703.

Obesity with Temporary Hypogenitalism.—Cerviño studied children between the ages of 7½ and 14 years, nine of whom were boys, in whom obesity was associated with hypogenitalism. Some of the cases presented symptoms resembling Fröhlich's syndrome; others were differentiated from the Fröhlich type by a generalized distribution of adipose tissue and an exaggerated development of bones and muscles. Others again belonged to an intermediate type. Hypogenitalism in the cases simulating Fröhlich's syndrome was restored to normal conditions at puberty or later if retardation of puberty occurred. The various features of the clinical picture including personal and familial antecedents, age of onset, evolution, genital pathology, secondary sex characteristics and gynecomastia are discussed. Obesity with hypogenitalism dissimilar to Fröhlich's syndrome was found to date from birth or develop with the growing child and was found to continue after puberty and was observed either to undergo no modifications or to increase or decrease. In these patients the head was large, the cheekbones and chin pronounced and the diameter of the thorax and pelvis large for the age and the body build. The feet gave the impression of a flatfootedness that was only infrequently confirmed roentgenologically. Heredity played a significant part. There was also precocity in dentition and in the ability to walk and talk. The general health was good. The appetite was exaggerated but did not show the predilection for certain foods noted in the cases resembling the Fröhlich type. Laboratory tests indicated normal levels of glycemia or a tendency to hyperglycemia. The author regards obesity with hypogenitalism as due to modifications of the neurohypophysial system. While the destruction of the anterior lobe by itself has not been demonstrated to induce adiposity, almost always damage to the hypothalamus is concomitantly observed. Damage to the anterior lobe could produce hypogenitalism with low physical stature but not obesity. In the intimate connection between these two organs lies the explanation of many of the symptoms observed in these cases. The transitory cases resembling Fröhlich's syndrome may be due to damage done to the hypothalamus if the regulatory processes of fat, carbohydrate and water metabolism are lodged here. At the same time the function of the hypophysis (anterior lobe) may be normal or excessive. In retarded puberty cases there may exist a temporary hypofunction of the hypophysis. Cases unlike the Fröhlich syndrome in which, besides obesity, is also seen a pronounced development of bone and muscles and occasionally a temporary hypogenitalism suggest hypercorticalism. However, a functional increase of chromophil cells of the anterior pituitary may be involved. Restriction of carbohydrate and fat consumption gives better results in cases dissimilar to the Fröhlich type than in those resembling it.

Anovulation in Women.—Clinical observations of 142 cases of sterility within a three year period enabled Novak to detect thirty-nine cases (age level between 22 and 43 years) in which sterility was due to anovulatory cycles. Anovulatory cycles were noted four times out of ten in patients between 20 and 25 years,

four times out of eleven between 25 and 30, three times out of seven between 30 and 35, four times out of six between 35 and 40 years and four times out of five between 40 and 45 years. Endometrial biopsy, performed in nineteen of the thirty-nine cases within a few days before menstruation, disclosed a nonsecretory type of endometrium, with a proliferative activity that varied between clinical pictures corresponding to an early interval phase at one extreme and a marked Swiss cheese type of hyperplasia at the other. In eleven cases some degree of endometrial hyperplasia was encountered. In all cases menstruation was normal or approximately normal, though some showed a tendency to irregular tempo. In others the menstrual amount was above the average, though not pathologic. According to the author, failure of ovulation is to be considered a possible cause of sterility, especially in women approaching middle age. However, it is not usually advisable to perform endometrial biopsy repeatedly in women anxious to conceive lest it frustrate impregnation in a particular cycle. His observations tend to show that some women ovulate with some cycles and not with others, but that more frequently ovulation is likely to be completely in abeyance for considerable periods of time. Functional bleeding of the common type is merely an exaggeration of the anovulatory cycle. Since patients of this group exhibit no other evidences of endocrinopathy and are usually in good general health and since nonovulation may be a sporadic occurrence, therapeutic measures should be conservatively employed. Organotherapy with pregnancy urine preparations has not been successful. The effects of gonadotropic substances in pregnant mare serum on the human ovary have not yet been satisfactorily determined and require further investigation. The key to the riddle of why luteinizing fractions are released in some cycles and not in others seems to be locked up in the anterior pituitary.

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*Therapy of Eczema in Nurslings and Small Children. W. Bayer.—p. 243.
Treatment of Asthma with Injection of Serum of Own Blood During Childhood. G. Tamási.—p. 248.
Metrazol Intoxication in Children. T. Varga.—p. 251.
How to Supply Sick Nurslings with Breast Milk. H. Kleinschmidt.—p. 253.
Collaboration of Pediatrician in Diagnosis of Hereditary Defects. T. Brehme.—p. 259.

Therapy of Eczema in Infants.—Bayer reviews various measures employed in the treatment of the eczema of nurslings, giving special attention to the dietetic measures. He thinks that some of the failures in the dietetic treatment are due to the fact that the same diet which has proved effective in some cases is used for all cases and that local measures are neglected. He is in agreement with Rietschel that it is not so much the nature of a diet as the change of the diet that effects improvement. Brushing is a valuable adjunct to the local and dietetic measures. In a disorder in which it is customary to avoid all external irritation, brushing seems at first contradictory, although it has been recommended for the treatment of eczema in adults. The author employed brushing for the first time in the treatment of a child with mild ichthyosis. Salicylic petrolatum and brushing greatly improved the skin of this child. Then the brush treatment was tried on the infiltrated skin of chronic eczema and of neurodermatitis. Unexpected results were obtained. In acute eczema the healthy portions of skin are brushed. The process is continued until the skin becomes red. After the acute stage has been overcome and redness and weeping have disappeared, the eczematous areas are likewise brushed with greater caution in the beginning than are the healthy skin areas. Brushing is particularly effective in cases in which the acute inflammatory stage is rapidly followed by infiltration or in cases in which the skin has become firmly infiltrated and unelastic. From eight to fourteen days of systematic brushings, together with other local treatment, often produces astonishing results in these cases. At the onset of the treatment the brush should be rather soft and, as the treatment progresses, harder brushes are gradually employed. The brushing is done while the child is given its bath and is continued for about ten minutes. During the first few weeks olive oil or liquid petrolatum is added to the water of the bath. From 1 to 2 teaspoons of the oil is stirred into hot milk and the mixture is added to the bath water. The liquid petrolatum bath is helpful if the skin becomes rough. The brush treatment can be given in the ordinary water bath after the skin has become normal. The redness produced by brushing rapidly disappears and does not cause irritation leading to a flare-up of the inflammation. In addition to widening the capillaries and influencing the lymph stream of the skin, it can be assumed that the brushing also acts on the circulation. The increased blood perfusion of the skin doubtlessly increases the cutaneous metabolism.

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Ossification of Uterine Tubes. J. Foged.—p. 99.
Myoma and Carcinoma of Corpus Uteri. H. Leissner.—p. 106.
Clinical and Experimental Investigations on Hypophysial Transplantations. A. Westman.—p. 118.
*Case of Ectopia Cordis in Living Child, Born at Term. P. Kühnel.—p. 128.
Experiences with Scalp Forceps Traction in Treatment of Uterine Atony. P. Kühnel.—p. 139.
Luteinized Granulosa Cell Tumor. C. von Numers.—p. 146.
Curative Process in Ray Treatment of Uterine Cancer According to Stockholm Method. J. J. Chydenius.—p. 157.

Ectopia Cordis in Living Child Born at Term.—Kühnel reports an instance of abdominothoracoschisis with total ectopia cordis in a living child born nearly at term. The malformation consisted in a broad slitlike median defect of the upper part of the abdominal wall and the lower part of the thoracic wall through which the heart was protruding. The heart was beating with a normal rhythm and rate outside the chest. The child was delivered spontaneously in cephalic presentation and showed no other malformations. It lived twenty-six hours and died with increasing cyanosis and dyspnea. The necropsy revealed that from the anterior surface of the heart a thin cord extended down to the amniotic membrane of the umbilical cord. Microscopic examination revealed that this cord consisted of amniotic tissue. The abdominal part of the slit was from 5 to 6 cm. in width, but it was not open, being covered by a thin membrane which was made up of an inner peritoneal leaf and an outer amniotic membrane. The thoracic part of the defect ended a little proximally to the middle of the sternum. The anlage of the sternum was defective, only the nucleus of the manubrium and the upper body nucleus being demonstrable. Only the three upper ribs were connected with the sternum. Opinions differ about the cause and development of the congenital ventral defects, but it is generally agreed that the development of these defects begins early in fetal life. The author emphasizes that a distinction has to be made between hernia proper, most often an umbilical hernia with its characteristic hernial sac, and the true cleft malformation, which either is entirely devoid of a sac or in which, as in the reported case, there is merely a thin covering consisting of peritoneum and possibly some amniotic elements. The term "congenital umbilical hernia" the author applies only to the true hernias, in which a greater section of the intestine, perhaps together with other abdominal organs (stomach, liver, and so on), is situated in the hernial sac. In the cleft defects the eventrations usually are far larger and more variegated. Morphologically and genetically these two conditions differ. Umbilical hernia involves the persistence and growth of the hernial anlage that is a physiologic phenomenon in early embryonic life. Up to the ninth to tenth fetal week there is always an intestinal loop present in the umbilical pouch on the abdominal wall. When the abdominal cavity becomes more spacious the entire length of the intestine is again withdrawn into the abdominal cavity. When this retraction of the intestine into the abdominal cavity is not complete, the result is "physiologic" umbilical hernia. Incomplete closing of the anterior body wall is a true malformation. Little is known about the etiology of these congenital defects, but it can be established that the incomplete fusion of the fetal abdominal wall originates early (about the fourth week) and that these defects are rare. It has been estimated that, whereas a large congenital umbilical hernia is seen about once in 5,000 fetuses, a cleft abdomen is seen only once in 17,000 and the combined abdominothoracic defect is even more rare.